21 March 2024
EMA/169039/2024
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Jubbonti

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/005964/0000

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List of abbreviations

ADCC	Antibody-dependent cell-mediated cytotoxicity
AP	Acidic peak
API	Active pharmaceutical ingredient
AUC	Analytical ultracentrifugation
AUC	Area under the curve (pharmacokinetics)
BP	Basic peak
CAP	Protein A affinity chromatography
CD	Circular dichroism spectroscopy
CEC	Cation exchange chromatography
CEX	Cation exchange chromatography
CPP	Critical process parameter
CQA	Critical quality attribute
CZE	Capillary zone electrophoresis
DS	Drug substance
DSP	Downstream process
DP	Drug product
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
Fc	Fragment crystallizable
FcRn	Neonatal Fc receptor
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FL	Fluorescence detection
IgG	Immunglobulin G
IRT	Interactive Response Technology
KPP	Key process parameter
LISY	Liquid in syringe
LIVI	Liquid in vial
mAB	Monoclonal antibody
MAC	Multimodal chromatography
MCB	Master cell bank
MS	Mass spectrometry

NP-HPLC	Normal phase high performance liquid chromatography
NP-HPLC-FL	Normal phase high performance liquid chromatography fluorescence detection
nrCE-SDS	Non-reducing Capillary electrophoresis using sodium dodecyl sulfate non-gel sieving
nrPepMap	Non-reducing peptide mapping
PK	Pharmacokinetics
PPCB	Post production cell bank
Prolia EU	EU-authorized Prolia®; the registered trademark sign "®" will be omitted for Prolia throughout the text of this document
Prolia US	US-licensed Prolia®; the registered trademark sign "®" will be omitted for Prolia throughout the text of this document
QA	Quality attribute
QTPP	Quality target product profile
RANKL	Receptor activator of nuclear factor kappa-B ligand
RGA	Reporter gene assay
rCE-SDS	Reducing Capillary electrophoresis using sodium dodecyl sulfate nongel sieving
rPepMap	Reducing peptide mapping
RP-HPLC	Reverse phase high performance liquid chromatography
SEC	Size exclusion chromatography
SOP	Standard operating procedure
SPR	Surface plasmon resonance
USP	Upstream process
WCB	Working cell bank
Xgeva EU	EU-authorized Xgeva®; the registered trademark sign "®" will be omitted for Prolia throughout the text of this document
Xgeva US	US-licensed Xgeva®; the registered trademark sign "®" will be omitted for Prolia throughout the text of this document

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sandoz GmbH submitted on 25 April 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Jubbonti, 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:

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Jubbonti 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, Jubbonti 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;

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 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

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

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

- Product name, strength, pharmaceutical form: 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

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
10 November 2016	EMEA/H/SA/3409/1/2016/III	Peter Mol, Kirstine Moll Harboe
9 November 2017	EMEA/H/SA/3409/2/2017/III	Rune Kjeken, Juha Kolehmainen
13 December 2018	EMEA/H/SA/3409/2/FU/1/2018/III	Juha Kolehmainen, Andrea Laslop
27 January 2022	EMA/SA/0000067538	Juha Kolehmainen, Elina Rönnemaa

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

The strategy with regards to the comparability assessment, the need for preclinical studies, the design of the supporting clinical studies, the extrapolation of the study results to all authorised indications of the reference product, and the overall adequacy of the clinical development programme.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Christian Gartner Co-Rapporteur: Kristina Dunder

The application was received by the EMA on	25 April 2023
The procedure started on	18 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	3 August 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 August 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 November 2023
The following 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:	
– A routine GCP inspection at 3 sites in Bulgaria, Germany and Japan between 02 October and 01 December 2023. The outcome of the inspection carried out was issued on 25 January 2024.	20 July 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	22 December 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 January 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 January 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	6 March 2024
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 Jubbonti on	21 March 2024

2. Scientific discussion

2.1. Problem statement

Not applicable for biosimilars.

2.2. About the product

Jubbonti 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

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.

2.3. Type of application and aspects on development

During the development of Jubbonti (GP2411), the applicant sought scientific advice from the EMA Scientific Advice Working Party (SAWP) four times. All aspects that were discussed critically during these advice procedures and are deviating from the final study designs are discussed in the respective methods or result sections.

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

- Ranges of active pharmaceutical ingredient-related quality attributes for drug product comparability assessment.
- Panel of physicochemical, biophysical, and biological methods for demonstration of comparability and extended characterization to support the comparability assessment.
- Criticality assessment of quality attributes after technical proof of similarity between GP2411 drug substance and the reference product.
- Final similarity evaluation of selected quality attributes.
- Comparability strategy to support a transfer of drug substance manufacturing to the commercial facility and scale up of drug product liquid in vial (LIVI) and drug product liquid in syringe (LISY) manufacturing processes at the commercial facility; updated approach for the comparative assessment of quality attributes.
- Proposal not to conduct any in vivo animal pharmacology and toxicology studies.
- Proposal not to perform a functional antibody-dependent cell-mediated cytotoxicity (ADCC) assay.
- Design of a single pivotal clinical PK/PD, efficacy, safety, and immunogenicity study comparing GP2411 and the reference product in women with postmenopausal osteoporosis including primary endpoint, sensitivity of baseline-normalized serum CTX biomarker, equivalence margin, dosing regimen.
- Design of a Phase III efficacy and safety study comparing GP2411 and Prolia in women with postmenopausal osteoporosis including study population, dosing, primary endpoint and secondary endpoints, equivalence margin, choice of comparator.

- Design of a comparative, randomized, parallel-arm, double-blind clinical trial in women with postmenopausal osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity of GP2411 and EU-authorized Prolia including wash-out rules for prior osteoporosis treatment and other bone-active drugs, age stratification, primary pharmacodynamic endpoint, strategy to optimize PK, PD, and anti-drug antibody sampling time points.
- Design of a 3-way PK and PD similarity study comparing GP2411, the EU-sourced, and the US-sourced reference product including study population, dosing, primary and secondary endpoints.
- Design of a comparative, randomized, controlled, double-blind clinical study with three parallel arms to establish 3-way PK and PD similarity between GP2411, Xgeva-EU, and Xgeva-US in healthy male volunteers including newly proposed dosing, PK and immunogenicity sampling time points, blinded sample size re-assessment, primary pharmacodynamic endpoint.
- Separate hierarchical testing strategies in a PK and PD 3-arm parallel study comparing GP2411 with Xgeva-EU and Xgeva-US (CGP24112101); separate hierarchical testing strategies in a randomized, double-blind, multicentre integrated Phase I/III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity of GP2411 and Prolia-EU (CGP24112301); need for population PK modelling to support the assessment of PK similarity between GP2411 and the reference product.
- Extrapolation of GP2411 clinical study results to all authorized indications of the reference product.
- Adequacy of the overall clinical development programme.

2.4. Quality aspects

2.4.1. Introduction

Jubbonti (internal code: GP2411) is a proposed biosimilar to the reference medicinal product Prolia. The active substance denosumab is a genetically engineered human IgG2 kappa monoclonal antibody directed against the transmembrane or soluble receptor activator of nuclear kappa-B ligand (RANKL). Of note, the active substance of Jubbonti and Wyost, which is submitted simultaneously as proposed biosimilar to Xgeva, is identical.

The finished product, GP2411, liquid in syringe (LISY), is presented as solution for injection containing 60 mg/1.0 mL of denosumab as active substance.

Other ingredients are: glacial acetic acid*, sorbitol (E 420), polysorbate 20, sodium hydroxide (for pH adjustment)*, hydrochloric acid (for pH adjustment), water for injections.

*acetate buffer is formed by mixing acetic acid with sodium hydroxide

The finished product is supplied in one strength (60 mg/mL) in a single-use pre-filled syringe, consisting of a Type I glass barrel equipped with a stainless steel 29 Gauge needle, a fluoropolymer coated rubber stopper and a needle shield assembled with a needle safety device.

2.4.2. Active substance

2.4.2.1. General information

The active substance (INN: denosumab) of GP2411 is a genetically engineered human IgG2 kappa monoclonal antibody directed against the transmembrane or soluble receptor activator of nuclear factor kappa-B ligand (RANKL). The average molecular mass of the intact (0K variant, oxidised cysteines), aglycosylated form of denosumab is 144,460 Da.

Denosumab is composed of two heavy chains (HC) and two light chains (LC) of the kappa subclass, and contains 36 total cysteine residues, which are involved in formation of both intra-chain and inter-chain disulfide bonds. Each heavy chain contains a N-linked glycan at the consensus glycosylation site at asparagine 298. Each light chain contains 215 amino acids, with two intra-chain disulfides. Each heavy chain contains 448 amino acids, with four intramolecular disulfides.

A basic structural feature of human IgG2 antibodies is the formation of isoforms due to different arrangement of the disulfide bridges. The predominant isoforms of denosumab are A, B, and A/B.

The predominant oligosaccharides are bi-antennary complex type structures having zero or one terminal galactose and high mannose structures, namely mannose 5 (M5).

Binding of denosumab to RANKL neutralises the biological activity of RANKL by preventing RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells. Denosumab does not display Fc effector functions.

2.4.2.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The active substance (AS) is manufactured by Novartis Pharmaceutical Manufacturing LLC (formerly Lek Pharmaceuticals d.d.; Kolodvorska Cesta 27, 1234 Mengeš, Slovenia).

The AS is expressed in a CHO cell line. After thawing of WCB, cells are expanded in a series of inoculum preparation and pre-stage cultivation steps under controlled conditions. Upon transfer into the main stage bioreactor, cells are finally expanded and maintained under controlled conditions. The bulk harvest is clarified.

Denosumab is purified from the clarified, cell-free harvest using column chromatography steps. Subsequently, the AS is ultrafiltered/diafiltered, filtered through a filter, and filled into bottles. The bottles containing AS are stored under controlled conditions.

The manufacturing process includes two dedicated, orthogonal virus clearance steps, i.e. low pH treatment and virus filtration.

The description of the manufacturing process and its controls is satisfactory.

Control of materials

No animal- or human-derived materials are used for manufacture of GP2411 DS. The information provided on raw materials and process materials is sufficient.

The information regarding the expression vector, development of the final production cell line, and establishment of the two-tiered cell bank system with Master Cell Bank (MCB) and Working Cell Bank (WCB) is satisfactory. The parental host cell line was transfected with the expression vector and the final clone was selected in two clone screening rounds. Monoclonality of the final production clone was

ensured by two rounds of cloning, i.e. initial single cell cloning and limiting dilution cloning of the final selected clone. The preparation of the cell banks as well as their stability testing are described satisfactorily. The expression construct, cell substrate and cell banks (MCB, WCB, and PPCBs) have been characterised in accordance with ICH Q5A, Q5B and Q5D. An acceptable protocol for manufacture and qualification of new WCBs has been registered.

Process validation

A traditional approach was chosen to verify process performance at commercial scale. Prospective process validation encompassed manufacture of consecutive process performance qualification (PPQ) batches at the proposed commercial manufacturing site. In addition to the routine IPCs, additional testing was performed to monitor product variants as well as process- and product-related impurities. Confirmation of adequate removal of process- and product-related impurities and of hold times for process intermediate pools were part of the process validation activities at scale.

Overall, the results demonstrate that the manufacturing process performs consistently and delivers AS complying with the release specifications under commercial operating conditions.

Consistent removal of process-related impurities to acceptable low levels/below LOQ along the process steps and adequate control of product-related impurities (high molecular weight and low molecular weight variants) and product variants has been shown. The risk related to potential leachables is acceptably low. Additional spiking studies performed at small scale further demonstrate the capability of the process to remove residual DNA, leached Protein A, and high molecular weight (HMW) variants.

Hold times for process intermediates have been adequately validated under consideration of physico-chemical stability and microbial control in small-scale studies and were confirmed at scale.

The shipping process of AS from the AS manufacturing site to the FP manufacturers has been adequately qualified.

Manufacturing process development

The Applicant followed an enhanced development approach using existing knowledge on denosumab, process development and manufacturing experience, platform knowledge, risk assessment tools, and process characterisation (PC) studies to define a control strategy as outlined in ICH Q11. Quality attributes (QAs) were identified, and their criticality was determined under consideration of their impact on efficacy/biological activity, PK/PD, immunogenicity, and safety, and uncertainty about the impact assessment. Development data and PC studies were used to systematically evaluate process parameters regarding their impact on process performance and product quality and determine their acceptable ranges. A full design space is not claimed.

The small scale models (SSMs) used for the PC studies were adequately qualified. Overall, satisfactory summaries of the design and outcome of PC studies and related risk assessments are provided. The methodology applied for the risk assessments, definition of PC target ranges, and process parameter classification is deemed acceptable. The process parameters are classified into critical process parameters (CPP), key process parameters (KPP) and non-key (NKPP) process parameters. Their classification and acceptable ranges are adequately justified by the PC studies.

The overall control strategy for GP2411 AS includes multiple control elements that are grouped into three major categories, i.e. product understanding, process understanding, and commercial controls. For each CQA and other QA/PI important for monitoring process consistency multiple control elements are in place. In conclusion, the proposed overall control strategy appears adequate to ensure consistent product quality.

Three different AS manufacturing process versions, i.e. Process A, B, and C, were used throughout development. Process A was developed based on a platform process for monoclonal antibodies and scaled up after technical proof of similarity. For manufacture of clinical material, stability studies, and material for analytical similarity the process was transferred to the clinical manufacturing facility with various changes implemented (Process B). Subsequently, the AS process was transferred to the intended commercial manufacturing site as a process transfer (Process C). The process changes and adaptations introduced during development are sufficiently described and justified. Several minor changes have been implemented after PPQ. Considering the nature of these changes and available validation data, no additional validation activities or comparability studies are required.

Analytical comparability of AS manufactured according to Process B or Process C has been investigated in accordance with ICH Q5E. As Process A AS has not been used in clinical studies, relevant stability studies, for justification of specifications, or for demonstration of analytical similarity, demonstration of comparability between Process A and Process B is not required. Results of the analytical comparability study demonstrate that AS manufactured according to Process B or Process C are comparable. The observed minor differences are not expected to impact clinical performance of the product. Notably, Process B AS was manufactured at two different facilities at the same site, i.e. clinical batches were manufactured under GMP conditions, whereas non-GMP development batches were produced at another area at the same facility. Batches originating from the non-GMP development facility were used in the analytical biosimilarity exercise and to justify AS specifications. This facility mirrors the GMP facility; representativeness of the non-GMP development BPD batches has been sufficiently justified based on process, batch release, and additional characterisation data.

Characterisation

In accordance with the Guideline on development, production, characterisation, and specification for monoclonal antibodies and related products EMA/CHMP/BWP/532517/2008, the physico-chemical and biological properties of the AS were comprehensively characterised. Orthogonal, state-of-the art analytical methods were used.

Size, charge, disulphide, and glycation variants of GP2411 have been thoroughly characterised regarding their physicochemical and biological properties. Based on the results, aggregates and antibody fragments were classified as product related impurities.

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

Specifications

The release specification for GP2411 AS comprises tests for appearance, description, identity, purity and impurities, potency, quantity, bacterial endotoxins (Ph. Eur.) and bioburden (Ph. Eur.).

The set of quality attributes tested at release complies with ICH Q6B, Ph. Eur. monograph 2031, and EMA/CHMP/BWP/532517/2008.

The shelf-life specification is identical to the release specification except for the tests for identity and residual HCP which are excluded from the shelf-life specification. It comprises several stability-indicating methods. The stability-indicating capability of these methods has been demonstrated during method validation and by forced degradation studies.

The acceptance criteria for the AS specification have been established under consideration of compendial requirements and regulatory guidelines, product characterisation, criticality of QAs, process development and characterisation, process validation, manufacturing experience, release and stability

testing results, clinical considerations, and statistical analysis. The AS specifications are aligned with FP release specifications. As no relevant changes of QAs have been observed during storage of AS at long-term conditions, acceptance criteria are identical for those parameters tested at release and for stability.

For justification of specifications, release and stability data for long-term conditions AS batches manufactured according to Process B or Process C were taken into account. The Process B batches include development batches manufactured at the non-GMP and batches manufactured at the GMP clinical facility.

Based on the release and stability results of the AS batches the applicant calculated one- or two-sided tolerance intervals to justify the proposed specification limits for quantitative parameters. In some instances, no statistical evaluation was performed due to discrete nature of data or insufficient number of data points. The proposed revised acceptance criteria are agreeable.

Analytical procedures and reference standards

Sufficiently detailed descriptions of the analytical methods have been provided for the non-compendial methods. Overall, the analytical methods appear adequate for their intended purpose. The capability of the stability indicating methods to detect product degradation/modification has been demonstrated adequately by forced degradation studies and during method validation. The implemented system suitability tests (SST) and sample acceptance criteria are suitable to provide adequate control over analytical method performance. The presented validations and verifications of the analytical methods are adequate and in accordance with ICH Q2(R1) and demonstrate the suitability of the analytical procedures for their intended use.

The history of the reference standards used throughout development of GP2411 is described satisfactorily. They were manufactured from GP2411 AS batches representing the respective development stage; at very early development stages pooled originator lots were used as reference standards. Recently, a two-tiered system with primary and working reference standards has been implemented. The reference materials were adequately qualified according to the development phase by release and additional characterisation tests. The procedures for assignment and stability monitoring of potency of the reference standards are acceptable and expected to prevent potential shifts. High consistency across the relevant reference standards is observed. Annual re-test results confirm stability of the previous standard and the current primary reference standard. The protocol for qualification and annual re-qualification of future primary and working reference standards is acceptable.

Batch analysis

Batch analyses data are available for the PPQ batches, post-PPQ GMP batches, and technical AS batches manufactured at the intended commercial site according to Process C. In addition, batch analyses data are provided for development batches and GMP batches (including the clinical batches used in the Phase I and Phase III studies) produced with Process B. All results comply with the specifications valid at time of testing and comply with the proposed commercial specifications (if applicable) as well. The presented results demonstrate that the manufacturing process reliably delivers GP2411 AS with consistent and acceptable quality.

Container closure

Gamma-sterilised 2 L bottles made of polyethylene terephthalate copolyester, glycol modified (PETG) with high-density polyethylene (HDPE) closure are used as container closure system for GP2411 AS. According to the applicant the materials of construction are in line with Ph. Eur. and USP monographs as applicable; the individual applicable monographs are listed in the dossier. Compatibility of container

closure system and AS has been confirmed by stability studies. Extractable studies demonstrate that the container closure system can be considered safe from a leachables perspective.

2.4.2.4. Stability

Based on the long-term stability data and a supportive statistical analysis the applicant claims an AS shelf-life.

Stability data are provided for AS batches stored at long-term conditions, accelerated conditions or stress conditions. Batches encompass GMP AS batches that were manufactured according to Process B at the clinical manufacturing facility and used/scheduled for clinical studies and PPQ batches manufactured at the commercial manufacturing facility according to the intended commercial process. In addition, final results of freeze/thaw (F/T) studies and photostability studies are available.

The design of the studies is in accordance with ICH Q5C, ICH Q1A, and ICH Q1B; statistical evaluations were performed according to ICH Q1E. Samples are stored in containers that are representative for the commercial container closure system described under 3.2.S.6. The analytical program follows the proposed AS specifications. The analytical method panel comprises stability indicating methods. Notably, the RANKL RGA was implemented at a later stage and hence, for the Process B batches only limited data are available for long-term conditions and no data are available for intermediate/accelerated conditions. However, as demonstrated by a bridging study, results of the RANKL ELISA and RANKL RGA are comparable.

At long-term conditions and at accelerated conditions, all results comply with the proposed commercial acceptance criteria and do not show any relevant trend (a minor decrease in certain purity/increase in impurity quality attributes is observed at accelerated conditions). At stress conditions, trends were observed for some quality attributes. Generally, the stability profiles of the batches are comparable at all storage conditions; minor differences between batches from Process B and Process C were observed regarding some quality attributes at accelerated and stress conditions.

Upon luminous exposure to 1210 klux h, various quality attributes of GP2411 were impacted. The effects were clearly less pronounced upon exposure to 495 klux h.

In conclusion, the presented data support the proposed shelf life, when stored in the container closure system defined in Module 3.2.S.6.

A commitment to complete the ongoing stability studies and to perform post-approval annual stability studies is provided.

2.4.3. Finished Medicinal Product

2 . 4 . 3 . 1 . Description of the product and Pharmaceutical Development

GP2411 60 mg/mL, liquid in syringe (LISY) (drug product; DP), which is developed as a proposed biosimilar to Prolia ®, is a sterile solution for injection containing Denosumab as active substance. The composition of GP2411 is similar to the one of the reference medicinal product (RMP). It is supplied in one strength (60 mg/mL) in a single-use pre-filled syringe, consisting of a Type I borosilicate glass barrel equipped with a stainless steel 29 Gauge needle, a fluoropolymer coated rubber stopper and a needle shield assembled with a needle safety device. The fill volume is including an overfill to ensure an extractable volume of 1 mL.

Other ingredients are: glacial acetic acid*, sorbitol (E 420), polysorbate 20, sodium hydroxide (for pH adjustment)*, hydrochloric acid (for pH adjustment), water for injections.

*acetate buffer is formed by mixing acetic acid with sodium hydroxide

The excipients used are of compendial quality. GP2411 drug product does not contain any excipients of animal or human origin or any novel excipients.

GP2411 LISY does not contain any stability or manufacturing overages.

Criticality of quality attributes has been assessed for both drug substance and drug product using an approach according to ICH Q9, which assesses each attribute regarding efficacy / biological activity, PK / PD, immunogenicity, and safety. Overall, the approach for identification of CQAs and the criticality assignment appears reasonable and sufficiently justified. The strategy for controlling of CQAs, relevant for the drug product, is deemed satisfactory.

Extensive formulation development studies have been performed during pharmaceutical development, justifying the appropriateness of using the same buffer formulation as the RMP. Analytical data from formulation screening studies have been presented. Primary packaging selection was addressed during development as well and respective analytical data have been provided.

The Applicant has provided an overview of the two processes, A and B, used for DP manufacturing so far. Both processes are claimed to be representative for commercial DP production. A comparative assessment between DP from both processes has been provided in section 3.2.R (Comparative assessment DP LISY). The extent of data of the comparability study is limited. No additional analysis beyond release and stability testing was performed. The Applicant has explained that the process changes have been assessed to have no relevant impact on product quality and thus, no prospective comparability protocol, no additional characterization and no IPC data had been generated. This (risk) assessment has not been provided. Whereas the data on release and stability do not indicate major differences between pre- and post-change batches, some minor differences concerning were noted. However, these differences seem to appear already at DS level of the used batches and are therefore considered acceptable for demonstration of DP comparability. Data provided in course of pharmaceutical development considered the upscaling with respect to mixing and filtration. As such the provided information on comparability between pre- and upscaled post-change GMP batches (at the same manufacturing site) is considered to be sufficient.

Studies to evaluate the appropriateness of process parameter (PP) settings were conducted for the DP manufacturing steps. Based on the evaluation of process steps potentially critical process parameters were further evaluated. Acceptable ranges (AR) were proposed for commercial manufacture for thawing of DS and manufacture of bulk DP and for manufacture of primary packaged product. PP categorized per criticality have been presented in tabular form along with the respective AR. All PP have been classified as either non-key PP or descriptive PP.

A study to assess adsorption of protein or polysorbate 20 to the filter used for sterile filtration did not indicate any adsorption.

The maximum physico-chemical and microbial hold times were evaluated. No relevant changes were observed in samples drawn after extended hold times and all values complied with release specifications. In addition, microbial challenge tests have been conducted on the compounded DP solution (post filtration) as well as on DS, PS20 stock and EDS to evaluate growth promoting effects and to support the microbial hold time during DP manufacture. Respective hold times are further discussed below.

Compatibility with process materials has been investigated in different studies. According to the information provided, tubings and filters appear compatible with the drug product. No substances of concern for patient safety are leaking into the product.

The proposed primary packaging materials are pre-sterilized and consist of a glass syringe barrel with a staked, stainless steel 29 G needle, a rubber plunger stopper and a rigid needle shield (RNS). Primary packaging materials coming into contact with drug product are of Ph. Eur. quality.

No substance of safety concern is leaking into the drug product as indicated by results of leachables and extractables testing. Elemental impurities were evaluated in line with ICH Q3D. No impurity of concern has been identified.

The drug-device combination product (DDC) consists of the following components: the pre-filled syringe with 60 mg/mL of GP2411 DP and in addition to the primary packaging, a needle safety device (NSD). The NSD consists of a needle guard and a plunger rod. The NSD does not come into direct contact with the drug product. The single-use device components and the medicinal product form a single integral product. During the procedure a major objection (MO) was raised due to the missing notified body opinion on the conformity of the integral device part with the relevant general safety and performance requirements set out in Annex I of the MDR (Medicinal Device Regulation (EU) 2017/745). The requested notified body opinion has been provided upon request and the MO is considered to be resolved.

Suitability of the primary packaging has been adequately evaluated by the applicant. Suitability for shipping including stopper movement at low air pressure was confirmed in a study.

Suitability of the DDC was evaluated under consideration of indication, intended users, route of administration and injection site, dose setting and administration. Risk management and human factors engineering activities have been performed. In course of the design verification, extractable volume; break-loose and extrusion force (BLE); biocompatibility; stability of the PFS, device components and DDC; and suitability for shipping was evaluated. In course of the design validation a human factors engineering activities in line with IEC 62366-1 have been performed.

No reconstitution or dilution is foreseen prior to administration by injection. Compatibility of GP2411 DP with its excipient and primary packaging materials has been shown in formulation studies and confirmed by stability data. Spiking studies focusing on tungsten and silicone oil leachables were performed in order to confirm compatibility of the DP with the primary packaging material.

The information provided under section Pharmaceutical Development is mostly sufficient.

2.4.3.2. Manufacture of the product and process controls

The manufacturers of GP2411 LISY drug product are appropriately listed and manufacture is performed at qualified GMP facilities. Valid GMP certificates and/or manufacturing authorizations have been provided for all drug product manufacturing sites.

The batch formula is adequately described.

The manufacturing process of GP2411 bulk drug product, based on standard pharmaceutical processing steps, includes thawing of the drug substance, manufacture of excipient dilution solution (EDS), compounding and microbial retention filtration, in-line sterile filtration, filling the final containers, stoppering and 100% visual inspection. After the filling operation the assembly, labeling and packaging of GP2411 LISY takes place (plunger rod, syringe label, needle guard, blister, packaging into folding box) to deliver the finished product. Information on hold times has been provided.; the maximum holding times have been investigated during process validation.

Critical steps during manufacturing of the GP2411 LISY DP have been identifies during manufacturing development. In general, adequate CPPs and IPCs have been implemented and described to ensure a controlled state of the manufacturing process and of DP quality attributes.

Automatic generation of batch numbers is briefly described. Overall, the provided information on the GP2411 LISY DP drug product manufacturing process is considered adequate.

Process validation was conducted on consecutive drug product batches. The manufacturing process validation covers the entire manufacturing process and was performed applying normal operating values/ranges.

Upon request the applicant has confirmed that no major deviation occurred during manufacturing of PPQ batches and has provided a summary on minor deviations, including description, root cause risk evaluation and respective corrective and preventive actions (if applicable), that occurred during process validation.

Based on the provided information sterile filtration can be considered as successfully validated.

Aseptic filling has been validated by media fills. The maximum filling time, covered through the media fills, has been added upon request.

The pre-fillable syringes and plunger stoppers are purchased ready to use. Adequate information on sterilization of the container closure system including name and address of sterilization sites, relevant ISO certificates of sterilization sites, sterilization methods and cycles and validation of sterilization cycles has been provided.

Hold times for the manufacture of GP2411 LISY DP were described and investigated through different studies.

Transport of GP2411 LISY DP with regards to mechanical stress has been validated/qualified. The product specific shipping verification included mechanical stress testing, including low air pressure, and evaluation of the samples for device functionality including container closure integrity and drug product quality. Upon request, further explanation on the concept of transport validation and additional details and data on the validation performed have been provided. No summary report on the performed shipping validation has been provided but a brief overview. It can be agreed that the validated shipping routes and shipping temperatures can be considered acceptable. Summer and winter conditions were also considered. During the validation defined shipping containers were used. The shipping container used for GP2411 remain unclear, however, the approach for qualification of shipping containers is adequately explained and as such the information provided is found acceptable.

2.4.3.3. Product specification, analytical procedures, batch analysis

The proposed finished product specifications includes respective acceptance criteria for release and shelf-life testing. The specification includes tests for appearance, description, identity, purity and impurities, potency, quantity, bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), sub-visible particles (Ph. Eur.), visible particles (Ph. Eur.), functional tests on the PFS and polysorbate 20 content.

The specification is in line with the requirements of general monographs Ph. Eur. 2031 (Monoclonal Antibodies for human use) and 0520 (Parenteral Preparations) as well as guideline ICH Q6B and EMA/CHMP/BWP/532517/2008 requirements.

They include two identity methods, both considered as being very specific, content in terms of total protein, purity/impurities, potency, microbial attributes (bacterial endotoxin (BET), sterility) and

general attributes. In addition, polysorbate 20 concentration, syringe functionality parameters and container closure testing are included in the specifications.

These development and changes, with regards to specifications, have been sufficiently described and are considered acceptable.

Mainly data on manufacturability from all batches, including PPQ, clinical and technical batches have been considered for justifying the proposed specifications. Availability of stability data, which have also been considered, are quite limited due to the ongoing studies. Information from process development, i.e., formulation development has been adequately taken into account. Clinical considerations were only provided for some of the quality attributes and no information on actual patient exposure have been provided (e.g. clinical batches used at a certain age). Statistical evaluation was done for the parameters where applicable. The applied statistical model has been described. The specifications applied are quite similar between DS and DP, which is found reasonable as limited manufacturing operations take place on the DP level.

In general, the setting of specification is adequately described and where applicable, comply with respective compendial requirements. Upon request the specifications for some quality attributes have been tightened. Additional justification has been provided during Day 120 response, which is acceptable.

In the main, sufficiently detailed descriptions on the analytical methods have been provided for the non-compendial methods. For compendial methods, the respective Ph. Eur. monograph has been added to the specifications under P.5.1. No method identifiers or respective SOP numbers were included, but for in-house methods hyperlinks were established and added to the specifications under P.5.1. in order to maintain a clear link between specifications, methods and methods validations.

The analytical methods appear adequate for their intended purpose and, in the main, the presented validation and verifications of the analytical methods specific for DP are adequate and in accordance with ICH Q2(R1).

Batch analyses data have been presented for DP PPQ batches and technical (non-GMP) batches manufactured, according to process B. In addition, data have been presented for clinical DP batches and one technical DP batch, manufactured according to process A. All batches complied with the pre-defined acceptance criteria valid at the time of release.

The primary packaging is a prefillable syringe (PFS) consisting of 1 mL type I borosilicated glass barrel of Ph. Eur. quality, with a staked stainless steel 29 Gauge needle, fixed to the syringe barrel with an adhesive; a grey fluoropolymer coated bromobutyl rubber stopper of Ph. Eur. quality, and a rigid needle shield (RNS) composed of a rubber needle shield complying with Ph. Eur. requirements covered by a rigid shell (not product contacting). The rubber needle shield encapsulates the needle whereas the rigid shell stabilizes and protects the closure. Further information has been provided on the supplier, name and catalogue number and description of the primary packaging components as well as supplier certificates and on the sterilization of primary container which are purchased "ready to use" (see above).

Suitability of the primary packaging has been adequately evaluated by the applicant including leachables/extractables evaluation (see section 3.2.P.2).

A plunger rod and, an off-the shelf needle safety device is assembled to the primary packaging. The plunger rod and the NSD are non-product contacting. The single-use device components and medicinal product form a single integral product. Upon request, the Notified Body Opinion report on the conformity of the integral device part with the relevant general safety and performance requirements

set out in Annex I of the Medicinal Device Regulation (EU) 2017/745 (MDR) has been provided and included in the dossier in section 3.2.R. The provided information is found to be sufficient.

2.4.3.4. Stability of the product

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC (36 months at 2-8°C) are acceptable.

The stability data provided by the applicant include data from technical batch, clinical batches, and long term stability data from process performance qualification (PPQ) batches. In addition, stability data from accelerated and stress studies have been provided for those batches.

The batches were tested against the stability specifications. In addition, for some quality attributes (QA) data were statistically evaluated by applying analysis of covariance (ANCOVA), which determines if there is a significant change over time for a certain QA. The clinical batches are included in the comparability study on clinical vs. commercial manufacturing process which was performed in course of upscaling from process A to process B. Based on this comparability study (please refer to comparability study report in section 3.2.R) the clinical batches can be considered as being representative of the PPQ/commercial batches. This comparability assessment is found to be acceptable (see DS part). Moreover, comparability is demonstrated between DS batches manufactured according to DS process B (clinical batches) and DS batches manufactured according to process C (PPQ batches). The comparability at the DP level between DP manufacturing process A and DP manufacturing process B has also been successfully demonstrated. As such and in accordance with Q5C and Q1A(R2) these small scale/pilot batches (technical and clinical batches) can be used as primary stability batches in order to support the shelf life.

At the intended storage condition of 2-8°C, all test results complied with the shelf-life specifications. At accelerated conditions minor changes are observed for stability indicating parameters. The slopes of the stability indicating methods of all tested batches are comparable. At the stress condition, tested batches showed a more pronounced degradation (compared to long-term and accelerated condition) reflected in decrease in purity and increase of product related impurities.

In addition to data from PPQ batches, data from syringe functionality testing, as part of the stability specifications, have been provided for the clinical batches and for the technical batch.

In summary, available real-time stability data have been provided for the PPQ batches. Full shelf-life real-time stability data have been provided for clinical batches and for technical batch. Syringe functionality data have been provided for the clinical and technical batch. Comparability between technical and clinical as well as between PPQ batches has successfully been demonstrated through respective studies at different levels of DS manufacturing and of DP manufacturing. As such, although small scale and non-GMP, data from the technical batch can be considered representative for the commercial process and supportive for the shelf-life claim. Thus, the currently proposed shelf life of 36 months at 2-8°C is supported.

The Applicant commits to conduct and complete the ongoing stability studies and a commitment for placing one batch of GP2411 LISY DP on long-term stability at the recommended storage condition every year that manufacturing of such batches occurs, has been included.

Overall, the presented stability studies are considered in line with ICH Q5C and ICH Q1A requirements. However, the OCs as outlined above should be sufficiently addressed and additional data from the ongoing stability studies should be provided prior to final assessment of the DP shelf-life.

2.4.3.5. Biosimilarity

GP2411 60 mg/mL solution for injection, liquid in syringe (Jubbonti, GP2411 LISY) and GP2411 120 mg/1.7 mL solution for injection, liquid in vial (Wyost, GP2411 LIVI) have been developed as biosimilars to the reference medicinal products (RMP) Prolia and Xgeva, respectively. The composition of the two GP2411 products is identical to the composition of the respective RMP. Due to the global development strategy of the applicant, analytical similarity of GP2411 was assessed in a comprehensive similarity exercise using EU-authorised as well as US-approved Prolia and Xgeva. Pooling of data for EU-Prolia and EU-Xgeva (and US-Prolia and US-Xgeva, respectively) has been previously agreed by the EMA (Procedure No. EMEA/H/SA/3409/2/2017/III) and is justified by a supportive study demonstrating comparability between all four originator products and publicly available information indicating that the active substance denosumab for all four originator products is manufactured by the same manufacturer. As discussed in a previous EMA scientific advice (Procedure No. EMEA/H/SA/3409/2/FU/1/2018/III), for active substance-related attributes the similarity assessment was mainly performed on GP2411 AS level to ensure inclusion of an appropriate number of independent GP2411 batches as multiple AS batches are pooled to manufacture a single FP lot (i.e. the FP lots cannot be considered independent) and only a limited number of GP2411 FP lots has been produced. A separate bridging report demonstrating that active substance-related QAs are not affected by the GP2411 FP manufacturing process has been provided. In addition, for those QAs where an impact of FP manufacture cannot be excluded and for the most relevant functional attributes, data of representative GP2411 FP lots have been included. Based on the presented data the applicant´s approach is deemed sufficiently justified and agreeable.

As part of the analytical similarity exercise an extended characterisation study was performed to further analyse and compare charge variants of a clinical GP2411 AS batch and a US-Prolia lot. As analytical comparability of GP2411 AS manufactured according to Process B or Process C and comparability of Prolia and Xgeva across both regions (i.e. EU and US) has been demonstrated this approach is deemed acceptable.

To further support the demonstration of biosimilarity between GP2411 and Prolia/Xgeva, a comparative forced degradation study was conducted. For this study, the degradation routes/stability profiles of FP lots each of GP2411 LIVI, GP2411 LISY, EU- and US-Xgeva, and EU- and US-Prolia (including pre- and post-shift RMP lots) exposed to various stress conditions were compared. Overall, GP2411 FPs and the RMPs exhibited a comparable degradation profile.

The approach and methodology of the analytical similarity assessment are described in detail. A separate report discussing the population in population similarity condition, potential exemptions from this condition, and the operating characteristics of the approach has been provided. For the main similarity study, the applicant applied quality ranges based on mean ± X SD to evaluate analytical similarity of GP2411 and the RMPs. The Applicant concluded that GP2411 and RMPs are highly similar if at least a certain percentage of the results for GP2411 are within the quality range for that attribute. Under consideration of criticality of the QA, risk of the QA (which takes into account its abundance), analytical method (variability, multiple methods for same QA), data distribution, the observed quality shift of the RMPs, and scientific considerations the multiplier X was adjusted accordingly for each individual QA. Notably, for several QAs (), a quality shift was observed for the RMPs. In these instances, the applicant applied quality shift quality ranges that were derived from pooled pre- and post-shift data and limited to the smallest possible quality range which covers both pre- and post-shift distributions. The Applicant justifies this approach with demonstrated safety and efficacy for both pre- and post-shift product by real-life use of the reference product and the expectation that the quality shifts display a non-relevant impact on safety and efficacy within the observed ranges. Considering the QAs affected by the quality shift and/or the extent of the shift (pre- and post-shift data populations are

overlapping), it is agreed that an impact on the clinical performance is unlikely. In addition, for the denosumab concentration in EU-Prolia, which was determined to be very tight, a widened quality range is proposed by the applicant. The Applicant justifies the widened quality range based on variability for Xgeva, variability observed for other EU-authorised biosimilar products, and clinical considerations. Whereas the proposed widening of the quality range is not fully endorsed, the applicant´s justifications that a larger variability of the active substance concentration in DP () is acceptable can be followed. Low risk QAs or QAs not amendable to quantitative analysis were assessed using a comparison of quantitative data or comparison of chromatograms, spectra etc., respectively. In summary, the evaluation approach and provided comprehensive justifications is in line with the current guidance as described in the revised Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017) and is deemed acceptable.

A sufficient number of independent GP2411 AS batches that were manufactured over a certain time span according to AS Process B or according to AS Process C were included in the analytical similarity assessment. Comparability of GP2411 AS manufactured with Process B or Process C has been demonstrated. Inclusion of technical AS batches manufactured according to Process B is sufficiently justified based on process, batch release, and additional characterisation data. In addition, data for GP2411 FP lots (GP2411 LIVI and GP2411 LISY) manufactured over a time span of 3 years according to FP Processes A or B at the respective DP manufacturing sites were included in the analytical similarity assessment. Comparability of FP produced with Process A or B has been demonstrated for both GP2411 LISY and GP2411 LIVI (please refer to the respective FP part). The AS batches/FP lots comprise technical/development, clinical, PPQ, and other GMP batches/lots. Considering the number of batches/lots and that material from different process versions manufactured over a certain period has been included, variability of the proposed biosimilar product appears to be sufficiently reflected.

A sufficient number of EU-Prolia (including lots used in the Phase 3 study) and EU-Xgeva (including lots used in the Phase 1 study) lots as well as US-Prolia and US-Xgeva (including lots used in the Phase 1 study) lots were analysed in the analytical similarity exercise. It is agreed that the number of lots sourced over sufficient time periods will provide a robust estimate of variability of the RMPs.

The selected comprehensive set of orthogonal state-of-the–art analytical methods, which covers primary and higher order structure, variants related to cysteine chemistry, charge, oxidation, glycosylation, or molecular size, and DP related attributes, as well as multiple biological functions mediated by the Fab or the Fc portion, is adequate to address the relevant quality attributes of denosumab. The Fab-mediated mechanism of action (MoA) was evaluated by a range of biological assays (binding to RANKL, neutralisation of RANKL and an osteoclast inhibition assay). Biological characteristics were further compared regarding interaction with FcγRI, FcγIIa , FcγIIb, FcγIIIa , FcRn, and C1q, and in terms of ADCC activity. In addition, binding selectivity was investigated using other TNF superfamily members, i.e. TNF-α, TNF-β, APRIL and BAFF. Overall, the descriptions and qualification data that have been provided for the analytical methods used for the analytical comparability exercise are considered sufficient and indicate that the methods are suitable for the intended purpose.

The study results and their evaluation are well presented in the dossier. Figures and tables showing the individual results and data distribution for each parameter, chromatographs, spectra, etc. have been included in the analytical similarity report. In addition, for each batch the individual analytical results are listed in a separate appendix.

Physicochemical characterisation

Primary and higher order structure

As demonstrated the amino acid sequence of GP2411 and Prolia/Xgeva is identical. Similar masses of the full antibody (main variants), the deglycosylated intact antibody, and deglycosylated reduced molecule, respectively, were determined by SEC-HPLC-ESI-MS for GP2411 and the RMPs. Certain differences are observed.

Spectra are superimposable for GP2411 AS/FP, Prolia and Xgeva. Highly comparable thermograms and melting points were obtained by differential scanning fluorimetry. Based on the data it is concluded that the higher order structure of the products is highly similar.

Cysteine chemistry variants

Compared to the EU-Prolia/-Xgeva, in GP2411 AS/FP slightly higher levels of free cysteines were determined. However, the levels are low and no differences in potency or higher order structure were observed between GP2411 and the RMPs. Thus, it is agreed that the minor difference is not clinically meaningful.

All expected disulphide bridges were identified in GP2411 FP and the RMPs. Analysis of the disulphide isoforms show the presence of the same isoforms in GP2411 AS/FP and the RMPs. Except for peak 5 (IgG2-A with increased level of free thiols) , the distribution of the isoforms was comparable. Of note, a quality shift leading to changed levels of the isoforms is observed for the RMPs and consequently, quality shift quality ranges were applied by the applicant (see above). The Applicant´s conclusion that the difference is not considered clinically meaningful as the difference is small and no impact on potency or higher order structure is observed is agreed upon.

Charge variants

Analyses show similar patterns with differences in the distribution of the charge variants: compared to the RMPs, less acidic and basic variants are present in GP2411 AS/FP. The charge variant profile is determined by various QAs of different criticality. Deamidation, glycation, glycine (G) to aspartic acid (D) misincorporation, fragments, and disulphide variants can be attributed to the acidic fraction; C-terminal lysine variants, aggregates, C-terminal proline amide, N-terminal pyroglutamate, fragments, disulphide variants are attributable to the basic fraction.

Extended characterisation show that overall, the distribution of the charge variants across the fractions was comparable between GP2411 and the RMPs. Minor differences in the acidic fractions were detected. For the basic fractions certain differences were observed. Overall, biological activity of the different fractions was comparable for GP2411 and RMPs. A slight difference for the acidic peak (AP) 4 and AP1 fractions is evident. However, high assay variability was observed and in addition, potential matrix effects are present and thus, these data should be interpreted with caution.

Analysis shows comparable profiles (notwithstanding minor differences) and pI values of the peaks for GP2411 AS/FP and the RMPs.

Analysis of GP2411 AS/FP and the RMPs by revealed slightly lower levels of N-terminal pyroglutamate light and heavy chain and slightly lower levels of C-terminal lysine. Levels of these variants were generally low. The content of C-terminal proline amide was between the pre- and post-shift levels determined for the RMPs. Compared to the RMPs, the extend of deamidation was lower for GP2411 AS/FP. The observed small differences are not expected to impact clinical performance of the product.

Low level G to D misincorporations were identified at various positions of heavy and light chain of GP2411 and RMPs with slightly higher rates observed. Except two positions that were only identified for GP2411, all other G to D misincorporations were also found in the RMPs. Taking into account the result of the Phase 3 study and that no impact on biological activity is evident, the applicant´s position that the observed differences are irrelevant with regard to safety and efficacy can be accepted.

The level of glycation of GP2411 AS/FP is higher compared to the amount found in the pre-shift or post-shift RMPs, respectively. The glycation pattern is identical between GP2411 AS/FP and RMPs. As no effect on biological activity was observed and glycation is a natural modification of proteins it is agreed that no risk related to efficacy or safety is expected.

Oxidation variants

Less oxidation of methionine was observed for GP2411 AS/FP at the most susceptible positions Met106 (CDR3 of HC), Met253 (CH2 HC), and Met429, compared to Xgeva/Prolia. No oxidation of tryptophan, cysteine, tyrosine, or histidine was observed in GP2411 or the RMPs. The slightly lower rate of methionine oxidation is not expected to impact clinical performance of GP2411.

Glycosylation variants

Overall, analysis of the released N-glycans shows comparable glycan profiles between GP2411 and the RMPs. The main glycan structures are FA2, FA2G1 and M5. Except three glycans, all other glycan structures present in GP2411 were identified in the RMPs as well. The RMPs contain glycans that were not detected in GP2411. However, the levels of these glycans are low. Galactosylation levels are slightly higher for GP2411, whereas levels of afucosylation tend to be at the lower range observed for the RMPs. However, no difference between GP2411 FP and the RMPs was observed regarding binding to FcγRs, FcRn (binding of GP2411 AS was at the lower end of the activity seen for RMPs), or C1q. Sialylation of GP2411 is low but slightly higher compared to the RMPs. Compared to the RMPs where a quality shift was observed for high mannose variants, the level of high mannose glycoforms is more variable in GP2411 and stretches from slightly above to slightly below the range of the RMPs. However, the applicant´s justification that ADCC is not a relevant MoA for denosumab, only a negligible impact on PK is predicted based on an in-house PK model, and high mannose glycans are not immunogenic, and thus, the difference in high mannose glycans is not clinically relevant can be followed. This is confirmed by the two clinical studies showing similarity between GP2411 and the RMPs in terms of PK and efficacy.

Glycosylation site occupancy is generally high.

Size variants

N-terminal extensions due to incomplete cleavage of the signal peptide were only observed in the GP2411 heavy chain. The detected levels are low, both for total amount as well as for for the individual species. The Applicant stresses that no public information is available on the signal peptide for Prolia/Xgeva and hence, detection of incomplete cleavage of the signal peptide in the RMPs is technically extremely challenging. In addition, incomplete cleavage of the signal peptide has been reported for several marketed antibody products. Considering this, and the outcome of the clinical studies the presence of low amounts of variants with N-terminal extensions appears non-critical.

Comparable profiles with no new peaks in GP2411 were obtained. The content of LMW forms and HMW forms was slightly lower in GP2411. Additional results obtained are principally in line with the aforementioned results ; as expected, the level of HMW variants detected was generally higher with dimers being the main constituent. The slightly higher purity of GP2411 does not preclude biosimilarity.

FP related quality attributes

The denosumab concentration of GP2411 LIVI is comparable to the concentration determined for EU-Xgeva. For some GP2411 LISY lots, the concentration is beyond the range observed for EU-Prolia (but within the adjusted quality range proposed by the applicant – see above). However, the observed

variability for GP2411 LISY is within ± 5% (multiple EU-authorised antibody products show variability of ± 5% or more) and considered acceptable.

The theoretical extinction coefficient of denosumab has been experimentally confirmed using multiple Xgeva and Prolia lots. The experimentally determined extinction coefficient of GP2411 FP was comparable to the extinction coefficient of Xgeva/Prolia.

The extractable volume of GP2411 LISY and EU-Prolia is well comparable. Compared to EU-Xgeva, the extractable volume of GP2411 LIVI was slightly higher due to the slightly higher overfill implemented to ensure withdrawal of the 1.7 mL claimed in the label. This minor difference is considered acceptable.

Biological activity

Potency and target binding

GP2411 AS/FP and the RMPs show highly similar binding to RANKL. Sensorgrams for GP2411 and the RMPs are superimposable. Potency in terms of neutralisation of RANKL was comparable between GP2411 DS/DP and the RMPs. In one of the assays all batches (AS and FP) tested within the originator range with the exception of a single AS batch, in another assay all of the AS and FP samples tested within the originator range. Neither GP2411 DP nor the RMPs interacted with other TNF superfamily members TNF-α, TNF-β, APRIL and BAFF; the corresponding sensorgrams are essentially identical.

Interaction with FcγRs of GP2411 FP and the RMPs was compared for a limited number of batches. Considering that denosumab exerts no Fc effector functions analysis of a small number of batches is acceptable. Binding to FcγIIa is highly similar between GP2411 FP and Prolia/Xgeva with comparable values. GP2411 DP and Prolia/Xgeva did not show a relevant interaction with FcγRI or FcγIIb. Affinity to FcγIIIa was very low; the sensorgrams for GP2411 FP and Prolia/Xgeva are highly comparable.

Binding activity of GP2411 FP to FcRn was comparable to Prolia/Xgeva; the presented sensorgrams are comparable. Binding activity of GP2411 AS was at the lower range/marginally below the originator range. This can be attributed to a residual matrix effect due to the different matrices of GP2411 AS and FP and the assay set-up. The comparative Phase I PK and PD study GP242101 and the Phase III study GP242301 revealed no differences in the PK profiles and PK parameters for GP2411 and EU-Xgeva or EU-Prolia, respectively.

Results of the ADCC assay that were performed with a limited number of lots confirm that neither GP2411 FP nor Prolia/Xgeva induce ADCC. Binding to C1q is comparable between GP2411 FP and Prolia/Xgeva; comparable dose-response curves are observed.

Overall, the presented results demonstrate that GP2411 and the RMPs are highly similar in terms of binding and functional activity.

In summary, biological activity and many physico-chemical attributes are highly similar between the proposed biosimilars GP2411 LISY/LIVI and the RMPs Prolia and Xgeva. The differences observed for various physico-chemical attributes and FcRn binding have been adequately justified by the applicant and are not expected to result in a different clinical performance of GP2411.

In conclusion, the totality of analytical data from the main analytical similarity study, the supportive studies, and the comparative forced degradation study demonstrate that GP2411 is analytically highly similar to the RMPs Prolia and Xgeva. The observed minor differences are not expected to impact clinical performance of GP2411.

Table 4 – Biosimilarity Exercise

Table 1 Physicochemical and biophysical results and similarity assessment of GP2411 and EU-approved Prolia/Xgeva

Quality attribute	Analytical method		Similarity assessment status***
Primary structure			
Amino acid sequence	rPepMap-MS		Identical
Molecular weight	SEC-MS		Identical
Cystein chemistry variants			
Free cysteins	Ellman's assay [mol/mol]		Slightly higher values
Disulfide variants/ isoforms	nrPepMap-MS		Identical
	RPC [%]		
		Peak 1	Highly similar
		Peak 2	Highly similar
		Peak 3	Highly similar
		Peak 4	Highly similar
		Peak 5	Slightly higher values for Peak 5

Quality attribute	Analytical method		Similarity assessment status***
Charge variants			
Sum of acidic and basic variants; Purity by charge	CZE [%]		
	Acidic variants		Lower values for GP2411
	Basic variants		Slightly lower values for GP2411
	Main variant		Higher values for GP2411
pI	iCE		Highly similar
Deamidation	rPepMap-MS [%]		Lower values for GP2411
Sequence variants (G to D)	rPepMap-MS [%]		Slightly higher values for GP2411
N-terminal pyroglutamate	rPepMap-MS [%]		
	LH1 pE		Lower values for GP2411
	LL1 pE		
C-terminal lysine	rPepMap-MS [%]		Lower values for GP2411
C-terminal proline amide	rPepMap-MS [%]		Similar values

Quality attribute	Analytical method	Similarity assessment status***
Glycation (Amadori product)	SEC-MS [mol/mol] mAb	Higher values for GP2411
	Elucidation of site-specific glycation via rPepMap-MS	Similar values
Oxidation variants		
Methionine oxidation	rPepMap-MS [%] $LH5M106_{ox}$ $LH11M253_{ox}$ $LH24M429_{ox}$	Lower values for GP2411
Glycosylation variants		
N-glycan site occupancy	rCE-SDS [%]	Similar values
N-glycan galactosylation	NP-HPLC-FL [%]	Higher values for GP2411
N-glycan sialylation NANA	NP-HPLC-FL [%]	Higher values for GP2411
Non-fucosylated N-glycans	NP-HPLC-FL [%]	Slightly lower values for GP2411
High mannose N-glycans	NP-HPLC-FL [%]	Higher values for GP2411

Quality attribute	Analytical method	Similarity assessment status***
Molecular size variants		
N-terminal extensions	rPepMap-MS [%]	Low amounts for GP2411 identified
Purity by size	SEC [%]	Highly similar
	nrCE-SDS [%]	Highly similar
Antibody fragments	nrCE-SDS [%]	Highly similar
Aggregates	SEC [%]	Highly similar
	AUC [%]	
	Dimers	Highly similar
	Multimers	Highly similar

Quality attribute	Analytical method		Similarity assessment status***
Higher order structure			
	CD		Highly similar
	FTIR		Highly similar
	DSF(T_m) [ºC]		Highly similar
DP related attributes			
API concentration	UV content [mg/ml]		Highly similar Highly similar
Extractable volume	Weighing [mL]		Higher values for GP2411 Highly similar

Table -2 Biological characterization and similarity assessment of GP2411 and EU-approved Prolia/Xgeva

Quality attribute	Risk score[1)]	Analytical method	Similarity assessment status*
Main mode of action			
		ELISA [%]	Highly similar
		RGA [%]	Highly similar
		Osteoclast assay [%]	Highly similar
Target binding			
		SPR [%]	Highly similar
Binding selectivity			
		SPR [%]	Highly similar
Fcγ receptor binding			
		SPR [%]	
		FcγRI	Highly similar
		$FcγRIIa_{His131}$	Highly similar
		$FcγRIIa_{Arg131}$	Highly similar
		$FcγRIIIa_{Phe158}$	Highly similar
		$FcγRIIIa_{Val158}$	Highly similar
Neonatal Fc receptor binding			

Quality attribute	Risk score[1)]	Analytical method	Similarity assessment status*
		SPR [%]	Highly similar for GP2411 FP, AS tests at the lower end
ADCC			
		Surrogate assay	Highly similar
C1q binding			
		ELISA	Highly similar

2.4.3.6. Post approval change management protocol(s)

In a post approval change management protocol (PACMP) Sandoz proposes a upscale of the GP2411 drug substance manufacturing process at the commercial manufacturing site to meet the anticipated patient demand for GP2411. The submitted PACMP for the planned upscale of the GP2411 AS manufacturing process at the commercial manufacturing site is acceptable.

2.4.3.7. Adventitious agents

Multiple complementing measures are implemented to ensure product safety with regard to non-viral and viral adventitious agents. The measures include selection and testing of materials, testing of cell banks and process intermediates, testing of microbial attributes as in-process controls and at release, implementation and validation of dedicated virus clearance steps and steps contributing to virus reduction. In addition, microbial quality is ensured by process design (microbial reduction filtrations, sterile filtration, aseptic processing) and adequate sanitisation procedures:

No raw materials of animal or human origin are used during manufacture of GP2411. Two recombinant materials, are used in the manufacturing process of GP2411 AS. Several consumables containing animal-derived materials are used in the GP2411 manufacturing process; these materials comply with the Note for Guidance EMA/410/01. The risk for TSE or viral contaminants is negligible

Endotoxin levels and bioburden/sterility are controlled throughout the manufacturing process and at AS and FP release.

Robust and effective overall virus clearance by four orthogonal manufacturing process steps has been demonstrated using validated down-scaled models. Two dedicated virus clearance steps, i.e. low pH treatment and virus filtration, as well as the multimodal chromatography step effectively reduce enveloped and non-enveloped viruses. In addition, Protein A chromatography contributes to virus clearance. Overall Log_{10} virus reduction factors of MuLV, PRV, Reo-3, and MVM were determined. The overall reduction $factor_0$ ensures clearance of retrovirus-like particles with a high safety margin.

In summary, the risk of potential contamination and transmission of bacterial, viral, or TSE agents appears to be adequately controlled and acceptably low.

2.4.3.8. GMO

Not applicable

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

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of

important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The notified body opinion on the conformity of the integral device part of the finished medicinal product with the relevant general safety and performance requirements set out in Annex I of the MDR (Medicinal Device Regulation (EU) 2017/745), has been provided, and thus, the major objection (MO) initially raised on the missing notified body opinion has been resolved.

For demonstration of biosimilarity, the applicant performed a sound and comprehensive analytical biosimilarity exercise. The totality of analytical data from the main analytical similarity study, the supportive bridging studies, and the comparative forced degradation study demonstrate that GP2411 (Jubbonti) is highly similar to the EU reference medicinal product Prolia. The minor differences observed for various physico-chemical attributes and FcRn binding are not expected to impact clinical performance of GP2411.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product (Jubbonti) is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Biosimilarity has been demonstrated versus the reference product Prolia. 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

Not applicable

2.5. Non-clinical aspects

2.5.1. Introduction

Analytical and functional similarity studies of Jubbonti and Prolia are described and discussed in the Quality section of the report. No additional non-clinical pharmacodynamics studies, neither in vitro nor in vivo, were performed by the applicant.

2.5.2. Pharmacology

No *in vivo* pharmacodynamics animal studies investigating analytical, physiochemical and functional similarity between Jubbonti and Prolia were conducted in addition to the analytical biosimilarity assessment.

2.5.3. Pharmacokinetics

Neither stand-alone comparative pharmacokinetics studies nor separate absorption, distribution, metabolism and/or excretion studies with Jubbonti and Prolia were performed by the applicant.

2.5.4. Toxicology

No non-clinical toxicological studies with Jubbonti were performed by the applicant.

2.5.5. Ecotoxicity/environmental risk assessment

According to the Guideline on the environmental risk assessment of medicinal products for human use – First version (EMEA/CHMP/SWP/4447/00 corr 2), in the case of products containing proteins as active pharmaceutical ingredient(s), an environmental risk assessment (ERA) should be provided, whereby this ERA consists of a justification for not submitting ERA studies, e.g. that due to the nature of particular pharmaceuticals they are unlikely to result in a significant risk to the environment. In line with this, the applicant provided a valid justification for the absence of ERA studies with Jubbonti, which is deemed acceptable.

2.5.6. Discussion on non-clinical aspects

Pharmacology

Jubbonti is a potential denosumab biosimilar. Denosumab is a full-length human monoclonal antibody of the IgG2 subclass, consisting of 2 heavy chains, and 2 light chains of the kappa subclass. There are two products approved in the EU including denosumab as API (Prolia and Xgeva). The indication for Prolia includes the treatment of PMO and the treatment of bone loss associated with hormone ablation in men with prostate cancer and in women with breast cancer. Xgeva is indicated for bone metastases from solid tumours, giant cell tumour of bone, and hypercalcemia of malignancy.

The Applicant performed a wide range of in vitro PD experiments comparing GP2411 activities and modes of action and FcR binding to EU-Prolia and/or EU-Xgeva of different sources. These experiments were performed for the similarity exercise which have been assessed in the quality part, showing good comparability with only minor concerns raised.

No *in vivo* pharmacodynamics animal studies investigating analytical, physiochemical and functional similarity between GP2411 and its referenced medicinal product Prolia (sourced from EU) were conducted in addition to the analytical biosimilarity assessment.

This is accepted and in agreement with the EMA Guideline on similar biological medicinal products (CHMP/437/04 Rev 1; 2014) and 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 Rev 1). In vitro assays may be considered paramount for the non-clinical biosimilar comparability exercise since they are generally more specific and sensitive in detecting differences between the biosimilar and the reference product.

For review of the biosimilar comparability exercise, please refer to the discussion and conclusions on the quality section above.

Pharmacokinetics

Neither stand-alone comparative pharmacokinetics studies nor separate absorption, distribution, metabolism and/or excretion studies were performed with GP2411 and Prolia.

PK similarity was examined in a clinical PK and PD study (CGP24112101), which is described and discussed in the Clinical section.

As stated in the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" [EMA/ CHMP/ BMWP/ 403543/ 2010]: If the comparability exercise in the *in vitro* studies is considered satisfactory and no factors of concern are identified, or these factors of concern do not block direct entrance into humans, an *in vivo* animal study may not be considered necessary.

Given the good comparability between GP2411 and EU-Prolia and/or EU-Xgeva on the analytical level, no further pharmacokinetic studies are deemed necessary.

The lack of these comparative studies in animal models was as well acknowledged and accepted in previous scientific advice in November 2016 (procedure number EMEA/H/SA/3409/1/2016/III) and in November 2017 (procedure number EMEA/H/SA/3409/2/2017/III).

Toxicology

Generally, studies regarding toxicology, including developmental and reproductive toxicity studies, are not required for non-clinical testing of biosimilars according to the EMEA/CHMP/BMWP/42832/2005 Rev1 guideline. Neither are studies regarding safety pharmacology, carcinogenicity and local tolerance. Scientific advice was provided by the EMA in November 2016 (procedure number EMEA/H/SA/3409/1/2016/III) and in November 2017 (procedure number EMEA/H/SA/3409/2/2017/III), supporting the proposed strategy of the applicant to not conduct any *in vivo* animal studies to assess biosimilarity between GP2411 and its reference product Prolia.

Therefore, and as there are no concerns arising from the analytical biosimilarity exercise triggering the need for in vivo studies, the absence of non-clinical toxicology studies conducted with Jubbonti is accepted and highly appreciated in regard to the principles of the 3Rs (EMA/CHMP/CVMP/3Rs/677407/2015).

Environmental Risk Assessment

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

Furthermore, denosumab is already used in existing marketed products (Prolia) and no significant increase in environmental exposure is anticipated.

In conclusion, Jubbonti is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, no concern was identified which would argue against a marketing authorization application. Overall, the CHMP considers that the non-clinical data provided by the applicant is considered adequate to support the approval of Jubbonti as a biosimilar to Prolia.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 3. Overview of clinical studies included in the GP2411 development program

Study no.	Study title	Number of subjects treated (SAF)	Duration of treatment and follow-up	Dosage
CGP24112101 (short: 101) Pivotal PK and PD study	Similarity between GP2411, EU-Xgeva and US-Xgeva in terms of PK, PD, safety, and immunogenicity Healthy male subjects	Total: N=499 GP2411: N=166 EU-Xgeva: N=171 US-Xgeva: N=162	Single dose Total duration: 39 weeks	GP2411 or EU-Xgeva or US-Xgeva 120 mg/1.7 mL single use vial Dosage for all 3 products: 35 mg as single s.c. injection
CGP24112301 (short: 301) Pivotal integrated PK, PD, confirmatory efficacy, safety and immunogenicity study	Similarity between GP2411 and EU-Prolia in terms of efficacy, PK, PD, safety and immunogenicity Female subjects with PMO	Total: N=527 **TP1:** GP2411: N=263 EU-Prolia: N=264 **TP2:** GP2411/GP2411: N=253 EU-Prolia/EU-Prolia: N=125 EU-Prolia/GP2411: N=124	3 doses every 26 weeks Total duration: 78 weeks, including 26 weeks follow-up after last dose	GP2411 or EU-Prolia 60 mg/mL PFS Dosage for both products: 60 mg, 3 s.c. injections, every 26 weeks, including a switch from EU-Prolia to GP2411 for the last dose for a subgroup of subjects

GP2411/GP2411: subjects who continued GP2411 treatment in TP2 of Study 301; EU-Prolia/EU-Prolia: subjects who continued EU-Prolia treatment in TP2 of Study 301; EU-Prolia/GP2411: subjects who switched from EU-Prolia to GP2411 at TP2 of Study 301

2.6.2. Clinical pharmacology

The overall clinical development program included 2 pivotal studies to demonstrate PK and PD similarity between GP2411 and Amgen's denosumab (Prolia/Xgeva).

• Study CGP24112101: The purpose of this study was to demonstrate PK and PD similarity in healthy male subjects between GP2411, EU-Xgeva and US-Xgeva, after a single s.c. dose of 35 mg denosumab.

• Study CGP24112301: The purpose of this study was to demonstrate similarity in PK, PD, efficacy and safety between GP2411 and EU-Prolia in female subjects with PMO. PK and PD parameters were evaluated as primary endpoints in this clinical setting after discussions with PMDA and EMA, respectively.

Apart from the above-mentioned studies, no other clinical pharmacology studies were performed.

2.6.2.1. Pharmacokinetics

Analytical Methods

PK ELISA:

The ELISA used for quantification of denosumab in human serum of healthy volunteers and patients with postmenopausal osteoporosis has been validated according to the guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009). All measured parameters were acceptable. The assay can be used as a method for quantification of GP2411DP LISY and LIVI as well as Xgeva®-EU, Xgeva®-US and Prolia®.

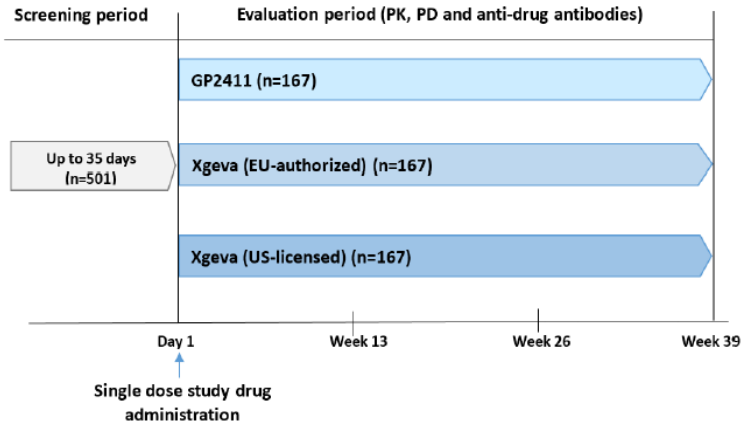
Overall, the PK ELISA for quantification of denosumab is found to be suitable for its intended purpose. Performance of the assay during clinical studies 101 and 301 is considered acceptable.

Study CGP24112101

Study design

This study was a two-centre, double-blind, randomized, three-arm, parallel-group, active controlled, single dose PK and PD similarity study and planned to be conducted in approximately 501 healthy male subjects. The study duration per subject was up to 44 weeks, consisting of a screening period of up to 5 weeks, 1 treatment day and a post-dosing assessment period of 39 weeks. Subjects were randomized in a 1:1:1 ratio (167 per treatment arm) to receive a single 35 mg s.c. dose of either GP2411 or Xgeva-US or Xgeva-EU, with the aim of having a minimum of 426 evaluable subjects (142 per treatment arm) at the end of the study. Randomization was stratified by weight category (≤69.9 kg, 70.0 to 79.9 kg, ≥80.0 kg), and by vitamin D replenishment (yes, no). The study design is depicted in the figure below.

Figure 1. Study design of Study CGP24112101



PK data analysis

Serum samples will be analyzed for free denosumab concentrations. PK parameters following a single s.c. dose of 35 mg study medication will be estimated using non-compartmental analysis (best-fit method) with Phoenix WinNonlin (Version 8.0 or above) by the pharmacokineticist of a CRO. For the determination of PK

similarity AUC_{inf}, AUC_{last} and C_{max} will be the primary parameters of interest. Tmax, Lambda_z, $AUC_{\%extrap}$ and $T_{1/2}$ will be calculated and reported as additional PK parameters. The PK parameters, together with the abbreviations and definitions are provided in the table below.

Table 4. Pharmacokinetic parameters

Parameter	Description
AUClast	The area under the serum concentration-time curve measured from the time of dosing to the last measureable concentration [ng x day/mL]
AUCinf	The area under the serum concentration-time curve measured from the time of dosing and extrapolated to infinity [ng x day/mL]
Cmax	The maximum observed serum concentration [ng/mL]
AUC%extrap	Percentage of AUCinf due to extrapolation from the time of the last observed concentration to infinity
Tmax	The time to reach maximum serum concentration [day]
Lambda_z	Terminal elimination rate constant [day^{-1}]
T1/2	Apparent terminal half-life [day]

Study participants

Inclusion Criteria

1. Signed informed consent obtained before participation in the study.

2. Male subjects aged 28 to 65 years (inclusive) at the Screening visit (Visit 1).

3. Physically and mentally healthy volunteers, as determined by the investigator based on medical history, physical examination, vital signs, ECG and safety laboratory results.

4. Body weight between 50.0 to 90.0 kg (inclusive) and BMI between 18.5 to 29.9 kg/m2 (inclusive) at Day −1 (Visit 2).

Exclusion Criteria (at screening visit 1)

1. Subjects with prior exposure to denosumab (Prolia, Xgeva, or biosimilar denosumab).

2. Previous exposure to any medication used for the treatment of osteoporosis (at any time point), or otherwise having an influence on bone metabolism (used within 1 year prior to study medication dosing).

3. Current hypocalcemia or hypercalcemia based on serum calcium at the Screening visit (Visit 1). Hypocalcemia was to be considered at serum calcium levels <2.10 mmol/L. Hypercalcemia was to be considered at serum calcium levels >2.65 mmol/L. Additionally, serum albumin values needed to be within normal limits (35.0 – 52.0 g/L).

4. Oral or dental conditions:

• Osteomyelitis or history and/or presence of ONJ

• Presence of risk factors for ONJ (e.g. periodontal disease, poorly fitting dentures, invasive dental procedures such as tooth extractions in 6 months before screening)

• Active dental or jaw condition which required oral surgery

• Planned invasive dental procedure.

A subject with suspicion of predisposing dental conditions in the opinion of the investigator was referred to a dentist for a professional dental examination. On the basis of the dentist's report, the investigator finally assessed this eligibility criterion.

5. Vitamin D deficiency (25 [OH] vitamin D serum level <20 ng/mL).

For subjects with vitamin D deficiency, a single attempt at replenishment with re-evaluation prior to randomization was permitted.

6. Subjects who had developed a fracture or had undergone an orthopedic surgery of bones other than the small bones of the hand and feet, within one year prior to screening.

7. Known diagnosis (present or historical) of hypo- or hyperthyroidism, whether controlled through treatment, or uncontrolled.

8. Known diagnosis (present or historical) of hypo- or hyperparathyroidism, whether controlled through treatment, or uncontrolled.

9. History of allergy to recombinant proteins, clinically significant food allergies (clinical significance according to the discretion of the investigator), hypersensitivity to any of the study medications (or calcium/vitamin D supplements), or hypersensitivity to any ingredients (including excipients) of the study medications (or supplements).

10. History and/or presence of clinically significant allergies and allergic reactions, including acute severe allergic reactions (e.g. anaphylaxis), moderate to severe allergies requiring medical treatment, and clinically significant latex allergy (clinical significance according to the discretion of the investigator).

11. A history of chronic diseases, which had the potential to interfere with the participation of the subject in the study, limit the study evaluation, or which may have jeopardized the subject in case of participation in the study. The investigator had to make this determination in consideration of the subject's medical history and/or clinical or laboratory evidence and needed to consider especially any chronic disease which might not have been obvious from the laboratory evaluations (e.g. pulmonary diseases, diabetes mellitus, autoimmune diseases, cardiovascular diseases).

12. Any surgical or medical condition that may have jeopardized the subject in case of participation in the study.

13. Significant illness, and/or acute infection which had not resolved within 2 weeks prior to screening (significant defined as per discretion of the investigator).

14. Recent (within the last three years) and/or recurrent history of autonomic dysfunction (e.g. recurrent episodes of fainting, palpitations, etc.), syncope, or fainting with phlebotomy.

15. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated.

16. Liver disease or liver injury as indicated by abnormal liver function tests. ALT (SGPT), AST (SGOT), GGT, alkaline phosphatase and serum bilirubin were tested. Elevation above 1.5-fold ULN for an isolated parameter amongst ALT, AST, GGT, alkaline phosphatase led to exclusion. Serum bilirubin was not allowed to exceed 1.2-fold ULN.

17. History or presence of impaired renal function as indicated by clinically significantly abnormal creatinine and/or urea values, or abnormal urinary constituents (e.g. albuminuria, clinical significance according to the discretion of the investigator), or presence of calculi.

18. Any other clinically significant laboratory abnormality of the laboratory parameters assessed as safety parameters (hematology, clinical chemistry, coagulation, urinalysis; clinical significance according to the discretion of the investigator).

19. Cardiac or cardiac repolarization abnormality, including any of the following detected at the Screening visit (Visit 1):

• Abnormal clinically relevant vital signs including systolic blood pressure below 90 or above 140 mmHg, diastolic blood pressure below 50 or above 90 mmHg, pulse rate below 45 or above 100 beats/min. In case pulse rate was less than 50 but equal to or more than 45, thyroid abnormality had to be excluded (based on medical history, physical examination and TSH level, judged for clinical significance by the investigator).

• History of myocardial infarction, angina pectoris, or coronary artery bypass graft within 6 months prior to dosing.

• Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block).

• Resting QTcF ≥450 msec at the Screening visit (Visit 1) or inability to determine the QTcF interval.

• Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia or any of the following:

• Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome.

20. History of immunodeficiency diseases, including a positive HIV test result.

21. Positive serology indicating Hepatitis B (present or past infections) or Hepatitis C infections

22. History of drug or alcohol abuse within the 12 months prior to dosing, or positive results for alcohol or drug tests conducted during screening. Any other history of drug or alcohol abuse assessed by the investigator that could interfere with the conduct of the trial will also lead to an exclusion from the study.

23. Use of any prescription drug and/or OTC medication (other than acetaminophen at a maximum dose of 2000 mg/day), within 2 weeks prior to dosing.

24. Use of other investigational drugs at the time of enrolment, or within 3 months or 5 half-lives at the time of dosing, whichever is longer.

25. Donation or loss of ≥500 mL of blood within 8 weeks prior to dosing, or longer if required by local regulation.

26. Plasma donation within 28 days prior to dosing.

27. Subjects who were known or suspected:

• not to have competence in speaking, writing and comprehending the local language, or not to be able to understand and comply with protocol requirements, instructions and protocol stated restrictions.

• not to be capable of understanding and evaluating the information given to them as part of the formal information policy (informed consent), in particular regarding the risk and discomfort to which they agree to be exposed to.

28. Subjects who were legally institutionalized or subjects under judicial protection.

29. Subjects who had an immediate family member (i.e., spouse, parent/legal guardian, sibling, or a child) who was also a member of study site staff or a member of the sponsor's study team.

Treatments

A single dose of 35 mg of either GP2411 or Xgeva-EU or Xgeva-US was administered s.c. at Day 1 (Visit 3). This dose was selected based on a modelling approach to optimize sensitivity and variability of PK and PD parameters and to provide an optimal setting for detecting potential differences between the administered medications.

GP2411, Xgeva-EU and Xgeva-US were supplied in single-use vials at a strength of 120 mg denosumab in 1.7 mL solution. GP2411 appeared as clear or slightly opalescent, colourless to slightly yellow or slightly brown solution as per technical specifications. Xgeva-EU and Xgeva- US appeared as clear, colourless to slightly yellow solution as per their label.

Outcomes/endpoints

The primary and secondary objectives and corresponding endpoints for the study are listed below.

Table 5. Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
To demonstrate 3-way PK similarity between GP2411, Xgeva-EU and Xgeva-US following a single subcutaneous injection of 35 mg to healthy male subjects	Serum PK parameters AUCinf, AUClast and Cmax
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To demonstrate 3-way PD similarity between GP2411, Xgeva-EU and Xgeva-US	• AUEC of %CfB in serum CTX
• To further compare GP2411, Xgeva-EU and Xgeva-US in terms of PD	• PD markers CTX and PINP in terms of serum concentrations per visit
• To evaluate safety of GP2411, Xgeva-EU and Xgeva-US	• Incidence of AEs, SAEs, related AEs (including AEs based on injection site reactions, vital signs, ECG and laboratory safety parameters)
• To evaluate the incidence of immunogenicity (ADA formation) against GP2411, Xgeva-EU and Xgeva-US	• Proportion of subjects testing positive for ADA

Sample size

The sample size was calculated based on a stepwise hierarchical testing strategy designed for FDA, where in each step comparisons for all three primary PK parameters were performed with 1) GP2411 vs. Xgeva-EU, 2) GP2411 vs. Xgeva-US and 3) Xgeva-EU vs. Xgeva-US. Success of step 1 (GP2411 vs. Xgeva-EU) was defined as sufficient for EMA.

Based on the assumptions presented in the table below, 142 evaluable subjects per treatment group were obtained. After accounting for 15% drop-outs, the total number to be randomized was calculated to be 501 subjects (167 per treatment group). The 15% drop-out rate included subjects that terminate prematurely, as well as subjects with protocol deviations that warrant their exclusion from the analysis of the primary endpoint. A sample size of 501 should provide an overall power of 90% for the study.

Table 6. Assumptions for sample size calculations

	Primary endpoints		Secondary endpoint
	AUCinf, AUClast	Cmax	CTX AUEC EMA+
Assumed distribution	Log-normal		
Equivalence margin	(80%, 125%)		
Coefficient of variation	46.1%	37.0%	24.0%
Two-sided alpha level	10%	10%	5%
Expected difference between treatment arms	5%	5%	5%
Correlation between the endpoints*	80%		0%
Pairwise power	90.6%	98.6%	>99.9%
Overall power	90%		
Drop-out rate	15%		

* Correlation between AUCinf and AUClast is assumed to be 100%; PK parameters and CTX AUEC are uncorrelated
+ CTX AUEC FDA endpoint will always be met if CTX AUEC EMA endpoint is met and therefore does not contribute to sample size calculations

The overall power to reach the secondary endpoint CTX AUC was higher than 99% with the given sample size.

Randomisation

At Day −1 (Visit 2), or in the morning of Day 1 (Visit 3), all eligible subjects were randomized via IRT to one of the 3 treatment arms in a 1:1:1 ratio.

Randomization was stratified by:

• weight category (≤69.9 kg, 70.0 to 79.9 kg, ≥80.0 kg)

• vitamin D replenishment (yes, no).

Blinding

This was a double-blind study. Subjects, investigators, most clinical site staff, CRO staff including blinded clinical monitors, and most members of the sponsor team remained blind to the identity of study treatment throughout the study. The exceptions from the blinding are indicated below.

The identity of the study medication in the vials could not be concealed as the appearance of the Xgeva and GP2411 vials differed. Drug product was therefore supplied in an unblinded manner. The following procedures ensured the blinding of the study treatment to study personnel administering the dose and performing the study assessments and to subjects:

• All unblinded study documentation, including any documentation identifying the treatment allocation, was kept strictly confidential until the time of unblinding, and was not accessible to anyone involved in the study, except the roles indicated below.

• Unblinded pharmacy/site staff not involved in any further study assessments prepared the syringes for the s.c. administration.

• The same type of syringe was used for the s.c. administration of any of the 3 study medications.

The exceptions from the blinding were:

• Unblinded pharmacy/site staff at the investigational sites

• Unblinded staff who entered unblinded data in eCRF (e.g. the medication number)

• Unblinded clinical monitors who reviewed unblinded information, i.e. drug accountability and correct treatment allocation at site, and performed monitoring activities with unblinding potential

• Unblinded sponsor staff who were involved in management and supply of study medications or interacted with unblinded site staff or unblinded clinical monitors

• Auditors, sponsor Quality Assurance staff and sponsor Compliance Clinical Operation staff were allowed to review unblinded information during audits, compliance visits or other activities conducted by them.

Unblinding of subjects, investigators, blinded site and sponsor staff was only permitted in case of subject emergencies and at the conclusion of the study.

Statistical methods

Analysis sets

In case of stratification errors recorded within the IRT (Interactive Response Technology) system, subjects were to be assigned in analysis to the strata according to the values reported in the clinical database.

Randomized analysis set: The randomized analysis set (RAS) included all subjects who were randomized to either GP2411, Xgeva-EU or Xgeva-US, including those who did not receive study treatment. The RAS was to be used for the description of study disposition.

Safety set: The safety set (SAF) included all subjects who received at least one dose of study treatment. Subjects were to be analysed according to the study treatment received. The SAF was used for the analysis of baseline and safety data.

PK analysis set: The PK analysis set (PKS) included all subjects who received study treatment, had at least one evaluable primary PK parameter (i.e. Cmax, AUClast or AUCinf) and completed the trial without any protocol deviation that had a relevant impact on PK parameters. Subjects were to be analysed according to the study treatment received and per strata as defined in the eCRF.

PD analysis set: The PD analysis set (PDS) included all subjects who received study treatment, had an evaluable AUEC of %CfB in CTX and completed the trial without any protocol deviation that had a relevant impact on CTX measurements or taking any other medication (excluding vitamin D and calcium intake), which may had a relevant influence on CTX. Subjects were analysed according to the study treatment received and per strata as defined in the eCRF.

Analysis of primary PK endpoints

The primary study endpoints were the PK parameters Cmax, AUClast and AUCinf.

The assessment of PK similarity was based upon the 90% confidence intervals for the ratio of the geometric means (GP2411 and Xgeva-EU) for Cmax, AUClast and AUCinf which had to be contained entirely within the pre-specified bioequivalence limits of 0.80-1.25.

If $\mu_{PK,T}$ and $\mu_{PK,R}$ denote the respective population means for test and reference of the PK parameters Cmax, AUClast and AUCinf, then the following null and alternative hypotheses were tested for the three parameters:

H0: $\mu_{PK,T}/\mu_{PK,R} \leq 0.80$ or $\mu_{PK,T}/\mu_{PK,R} \geq 1.25$ versus

H1: $0.80 < \mu_{PK,T}/\mu_{PK,R} < 1.25$

ANCOVA was performed on the log-transformed PK parameters. The ANCOVA model included treatment (GP2411, Xgeva-EU, Xgeva-US) as fixed factor and weight as continuous covariate. Stratification factor vitamin D replenishment (yes, no) was not expected to have a relevant impact on PK and was therefore not included in the model for PK.

Sensitivity analyses of primary PK endpoints:

If more than 10% of subjects in the SAF had protocol deviations leading to exclusion from the PKS, a sensitivity analysis based on the safety set was to be performed.

A sensitivity analysis was performed for the primary PK excluding the 35 subjects which were recruited before the outbreak of the COVID-19 pandemic (defined as before 01-Mar-2020).

Analyses of secondary endpoints

Descriptive summary statistics for serum CTX and PINP concentration data and the PD parameter AUEC of CTX were provided.

The assessment of PD similarity was based upon 95% confidence intervals of the ratio of the geometric means (test/reference) for the AUEC of %CfB in serum CTX concentrations, which had to be contained entirely within the prespecified acceptance margin of [0.80, 1.25].

If $\mu_{CTX,T}$ and $\mu_{CTX,R}$ denote the population means for test and reference of the AUEC, then the following null and alternative hypotheses were tested:

H0: $\mu_{CTX,T}/\mu_{CTX,R} \leq 0.80$ or $\mu_{CTX,T}/\mu_{CTX,R} \geq 1.25$ versus

H1: $0.80 < \mu_{CTX,T}/\mu_{CTX,R} < 1.25$

ANCOVA was performed on the log-transformed absolute AUEC. The ANCOVA model included treatment (GP2411, Xgeva-EU, Xgeva-US) as fixed factor, vitamin D replenishment (yes, no) as fixed factor and log-transformed baseline CTX value as a covariate. Stratification factor weight category (≤69.9 kg, 70.0 to 79.9 kg, ≥80.0 kg) was not expected to have a relevant impact on PD and was therefore not included in the model for PD.

A sensitivity analysis was to be performed for the similarity analysis of the secondary PD endpoint AUEC of %CfB in CTX excluding the 35 subjects which were recruited before the outbreak of the COVID-19 pandemic. This analysis was added in the SAP (version date 30 June 2022).

Participant flow

A total of 1137 subjects were screened, and 502 subjects were randomized in a 1:1:1 ratio to the treatment arms GP2411, Xgeva-EU, and Xgeva-US (see table below). Of those 502 subjects, 35 subjects were recruited before the start of the COVID-19 pandemic (defined as before 01- Mar-2020).

Similar numbers of subjects across all treatment groups completed the study (see table below). The 10 subjects who discontinued study participation included 3 subjects in the Xgeva-US group who discontinued study participation before treatment, due to randomization by mistake, 'Subject decision' and 'Physician decision', respectively.

Except for one discontinuation in the GP2411 group on Day 2 (lost to follow-up) and one discontinuation in the Xgeva-US group on Day 15 (subject decision), study discontinuations occurred at least 3 months after dosing (range: Day 87 – Day 170).

Table 7. Subject disposition (RAS)

Disposition/Reason	GP2411 N=166 n (%)	Xgeva-EU N=171 n (%)	Xgeva-US N=165 n (%)
Randomized subjects	166 (100)	171 (100)	165 (100)
Not treated	0	0	3 (1.8)
Treated	166 (100)	171 (100)	162 (98.2)
Completed	160 (96.4)	171 (100)	161 (97.6)
Discontinued study	6 (3.6)	0	4 (2.4)
Reason for discontinuation			
Adverse event	1 (0.6)	0	0
Lost to follow-up	2 (1.2)	0	0
Physician decision	1 (0.6)	0	1 (0.6)
Randomized by mistake without study treatment	0	0	1 (0.6)
Subject decision	2 (1.2)	0	2 (1.2)

A total of 180 subjects had at least one important protocol deviation (see table below). Protocol deviations occurred in more subjects in the Xgeva-EU group than in the GP2411 and Xgeva- US groups. The most frequently (i.e. ≥5% in any treatment group) reported protocol deviations were 'Study visit performed outside of allowed time window', 'PD sampling not performed between 7:30 and 10:00 am', 'Missed study visit', 'Calcium supplement intake not per protocol between Day −7 and Day −1' and 'Post-dose PK and/or PD sample on Day 1 taken outside of time limit'.

Recruitment

Study initiation date: 27-Jan-2020 (date of first ICF signing)

Study completion date: 09-Jun-2022 (last subject last assessment)

Database lock date: 19-Jul-2022 (clinical database), 08-Aug-2022 (re-lock of clinical database)

When the clinical database was declared to be complete and accurate, it was locked and unblinded. However, the clinical database had to be unlocked to correct treatment information for 2 subjects and to document an important protocol deviation in the eCRF (use of prohibited medication that could influence the bone metabolism). Unlocking of the database and implementing the updates had to be approved by the heads of relevant line functions (Data Operations, Biostatistics, Clinical Development Unit, Clinical Operations). After updating, the clinical database was re-locked.

Conduct of the study

The study protocol was amended 5 times: Amendment 1 (02-Aug-2019), Amendment 2 (07-Nov-2019), Amendment 3 (28-May-2020), Amendment 4 (03-Mar-2021), Amendment 5 (02-Apr-2021).

Baseline data

The demographics and baseline characteristics are presented in the table below.

Table 8. Demographics and baseline characteristics (SAF)

Demographic Variable	GP2411 N=166	Xgeva-EU N=171	Xgeva-US N=162
Age (years)			
n	166	171	162
Mean (SD)	47.0 (9.13)	44.5 (9.52)	46.0 (9.44)
Median	48.5	43.0	46.5
Min-Max	29-65	28-62	28-65
Ethnicity - n (%)			
Hispanic or Latino	1 (0.6)	1 (0.6)	0
Not Hispanic or Latino	162 (97.6)	170 (99.4)	162 (100)
Not reported	3 (1.8)	0	0
Race - n (%)			
Asian	1 (0.6)	2 (1.2)	0
-- Indian	0	1 (0.6)	0
-- Korean	1 (0.6)	0	0
-- Vietnamese	0	1 (0.6)	0
Black or African American	1 (0.6)	1 (0.6)	1 (0.6)
Multiple	1 (0.6)	1 (0.6)	0
White	163 (98.2)	167 (97.7)	161 (99.4)
Height (cm)			
n	166	171	162
Mean (SD)	179.5 (5.99)	179.2 (6.12)	178.5 (6.13)
Median	180.0	179.0	179.0
Min-Max	162-199	162-197	163-193
Weight (kg)			
n	166	171	162
Mean (SD)	79.89 (6.824)	80.06 (7.238)	79.26 (7.287)
Median	80.75	80.60	80.45
Min-Max	61.0-89.9	53.5-90.0	59.2-89.9
Weight category - n (%)			
≤69.9 kg	16 (9.6)	16 (9.4)	16 (9.9)
70.0 to 79.9 kg	61 (36.7)	63 (36.8)	60 (37.0)
≥80 kg	89 (53.6)	92 (53.8)	86 (53.1)
Vitamin D replenishment - n (%)			
No	106 (63.9)	108 (63.2)	102 (63.0)
Yes	60 (36.1)	63 (36.8)	60 (37.0)

Weight category and vitamin D replenishment were stratification factors.

Numbers analysed

The distribution of treatment groups was similar within each analysis set (see table below).

Table 9. Analysis sets – RAS

Analysis set	GP2411 N=166 n (%)	Xgeva-EU N=171 n (%)	Xgeva-US N=165 n (%)	Total N=502 n (%)
RAS	166 (100)	171 (100)	165 (100)	502 (100)
SAF	166 (100)	171 (100)	162 (98.2)	499 (99.4)
PKS	165 (99.4)	167 (97.7)	161 (97.6)	493 (98.2)
PDS	161 (97.0)	166 (97.1)	161 (97.6)	488 (97.2)

Reasons for exclusion from PKS and PDS

Overall, 9 subjects were excluded from the PKS and 14 subjects from the PDS, with similar distribution across treatment groups for both analysis sets (see table below). The most common reason for both analysis sets was that PK or PD parameter were "missing or excluded from analysis", i.e. they could not be calculated because samples were missing or had to be excluded because they were invalid.

Table 10. Reasons leading to exclusion from PK or PD analysis sets – RAS

Analysis Set / Exclusion reason	GP2411 N=166 n (%)	Xgeva-EU N=171 n (%)	Xgeva-US N=165 n (%)	Total N=502 n (%)
Excluded from PK Analysis Set (PKS)				
Total	1 (0.6)	4 (2.3)	4 (2.4)	9 (1.8)
Cmax, AUCinf and AUClast are missing or excluded from analysis	1 (0.6)	1 (0.6)	4 (2.4)	6 (1.2)
Visit 4 to Visit 7 concentration missing	1 (0.6)	0	2 (1.2)	3 (0.6)
pre-dose > LLoQ and > 5% Cmax.	0	1 (0.6)	0	1 (0.2)
Subject did not receive treatment at Day 1	0	0	3 (1.8)	3 (0.6)
Protocol deviations leading to exclusion	0	3 (1.8)	0	3 (0.6)
Excluded from PD Analysis Set (PDS)				
Total	5 (3.0)	5 (2.9)	4 (2.4)	14 (2.8)
AUEC value missing or excluded from analysis	5 (3.0)	1 (0.6)	4 (2.4)	10 (2.0)
Less than 3 valid required post-dose samples are available	4 (2.4)	0	2 (1.2)	6 (1.2)
Pre-dose sample missing	1 (0.6)	0	0	1 (0.2)
Pre-dose visit 3 result < 24% above LLoQ	0	1 (0.6)	0	1 (0.2)
Visit 3 pre-dose PK result above LLoQ	0	1 (0.6)	0	1 (0.2)
Subject did not receive treatment at Day 1	0	0	3 (1.8)	3 (0.6)
Protocol deviations leading to exclusion	0	4 (2.3)	0	4 (0.8)

PK outcomes and estimation study CGP24112101

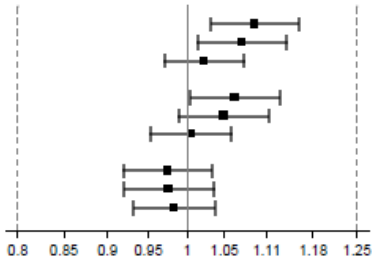
Primary PK analysis

The 90% Cis for the ratios (GP2411/Xgeva-EU, GP2411/Xgeva-US and Xgeva-EU/Xgeva-US) of geometric means for AUCinf, AUClast and Cmax were all contained entirely within the prespecified equivalence limits [0.80; 1.25] (see figure below).

Figure 2. Geometric mean ratio and 90% CI for primary PK parameters to compare treatments (PKS)

Treatment Comparison	Parameter	n1 (Test)	n2 (Reference)	Point Estimate	90% CI Lower	90% CI Upper
GP2411 vs Xgeva-EU	AUCinf (day*ng/mL)	162	167	1.09	1.03	1.16
	AUClast (day*ng/mL)	165	167	1.08	1.01	1.14
	Cmax (ng/mL)	165	167	1.02	0.97	1.08
GP2411 vs Xgeva-US	AUCinf (day*ng/mL)	162	161	1.06	1.00	1.13
	AUClast (day*ng/mL)	165	161	1.05	0.99	1.11
	Cmax (ng/mL)	165	161	1.00	0.95	1.06
Xgeva-EU vs Xgeva-US	AUCinf (day*ng/mL)	167	161	0.97	0.92	1.03
	AUClast (day*ng/mL)	167	161	0.98	0.92	1.04
	Cmax (ng/mL)	167	161	0.98	0.93	1.04

Forest Plot



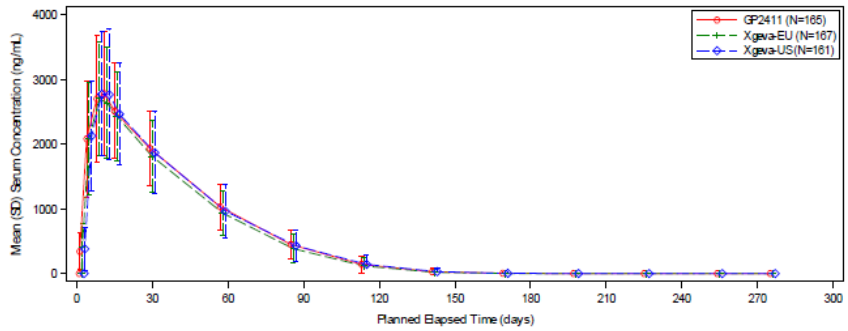
Fitting ANCOVA model to log of the PK parameter as dependent variable with treatment as a factor and weight as a covariate.
The dashed vertical lines indicate the equivalence limits of 0.80 and 1.25.

Serum Concentrations

The drug serum concentration time profiles (linear scale and semi-logarithmic scale) are provided in the figure below.

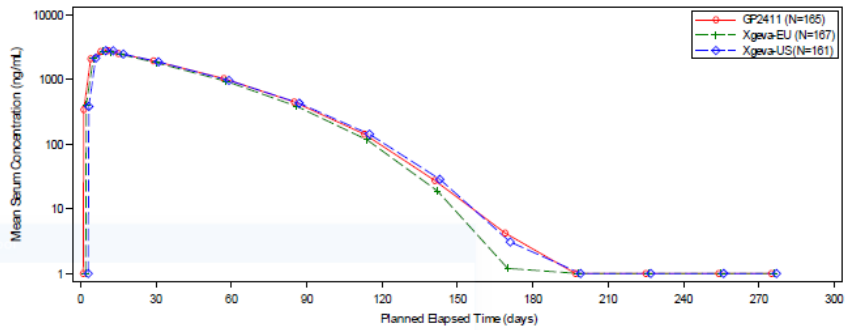
Figure 3. Drug serum concentrations – time profile (PKS)

Linear scale



A lower SD whisker is not displayed if mean-SD<0 since this is biologically implausible.

Semi-logarithmic scale



Values of 0 for which no log transformation is defined are presented as 1.

Summary Statistics of Pharmacokinetic Parameters

Summary statistics of all PK parameters, i.e. AUCinf, AUClast, Cmax, T1/2, AUC%extrap, Lambda_z and Tmax are provided in the tables below.

Table 11. Summary statistics for PK parameters – PKS

Parameter	Statistics	GP2411 N=165	Xgeva-EU N=167	Xgeva-US N=161
AUCinf (day*ng/mL)	n	162	167	161
	Mean (SD)	135000 (39600)	124000 (40000)	130000 (44800)
	CV%	29.3	32.2	34.5
	Geo-mean	129000	118000	122000
	Geo-CV%	32.5	35.6	36.6
	Median	136000	126000	125000
	Min-Max	41900-301000	39400-267000	35700-304000
AUClast (day*ng/mL)	n	165	167	161
	Mean (SD)	132000 (39900)	123000 (39900)	128000 (44900)
	CV%	30.3	32.5	35.0
	Geo-mean	125000	116000	121000
	Geo-CV%	33.9	35.9	37.4
	Median	134000	125000	122000
	Min-Max	41200-297000	39300-267000	35200-303000
AUC % extrap (%)	n	162	167	161
	Mean (SD)	1.60 (4.24)	1.23 (1.30)	1.36 (2.26)
	CV%	264.7	105.3	166.5
	Geo-mean	0.598	0.671	0.690
	Geo-CV%	233.4	186.1	187.6
	Median	0.663	0.802	0.753
	Min-Max	0.0422-40.0	0.0493-8.62	0.0488-24.7
Cmax (ng/mL)	n	165	167	161
	Mean (SD)	3050 (892)	2960 (817)	3070 (966)
	CV%	29.3	27.6	31.5
	Geo-mean	2910	2840	2920
	Geo-CV%	32.7	30.0	32.4
	Median	3040	2950	2950
	Min-Max	949-5970	775-5880	885-6890
Lambda z (1/day)	n	162	167	161
	Mean (SD)	0.0473 (0.0155)	0.0490 (0.0155)	0.0475 (0.0140)
	CV%	32.8	31.7	29.5
	Geo-mean	0.0449	0.0467	0.0455
	Geo-CV%	33.9	31.6	29.3
	Median	0.0446	0.0448	0.0445
	Min-Max	0.0172-0.0879	0.0265-0.0940	0.0229-0.0853
T1/2 (day)	n	162	167	161
	Mean (SD)	16.3 (5.54)	15.5 (4.65)	15.8 (4.46)
	CV%	33.9	29.9	28.1
	Geo-mean	15.4	14.8	15.2
	Geo-CV%	33.9	31.6	29.3
	Median	15.6	15.5	15.6
	Min-Max	7.89-40.3	7.37-26.2	8.12-30.3

n = number of subjects with evaluable PK parameters.
CV% = coefficient of variation (%)=sd/mean*100; Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100

Summary statistics for PK Tmax
PKS

Parameter	Statistics	GP2411 N=165	Xgeva-EU N=167	Xgeva-US N=161
Tmax (day)	n	165	167	161
	Median	9.99	9.96	8.04
	Min-Max	2.96-32.0	2.96-31.1	2.96-31.1

Study CGP24112301

Study CGP24112301 was a randomized, double-blind, multicentre, integrated phase I/III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity of GP2411 and EU-authorized Prolia.

The design and methods of study CGP24112301 are presented in section 3.3.4 "Clinical Efficacy". The PK results of this study are presented below.

Serum PK parameters AUCinf and Cmax after first dose

Serum PK parameter AUCinf and Cmax after the first dose are shown in the following table.

Table 12. Geometric mean ratio (GP2411/EU-Prolia) and 90% CI for PK parameters AUCinf and Cmax after the first dose (PKS)

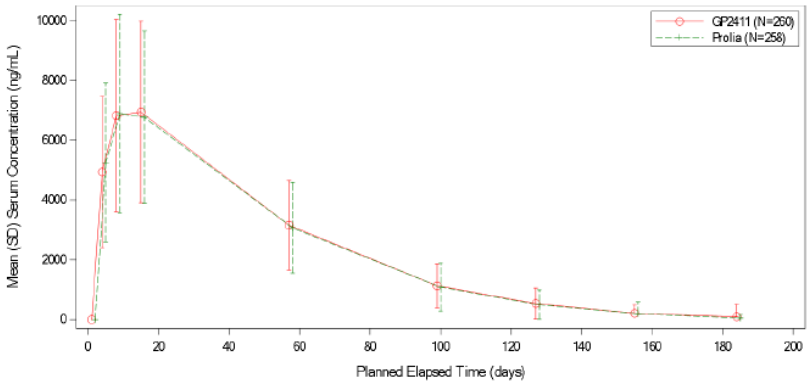
		Adjusted Geo-Mean				Geo-Mean Ratio GP2411/EU-Prolia	
Test vs Reference (Comparison)	Parameter (unit)	GP2411	n	EU-Prolia	n	Point Estimate	(90% CI)
GP2411 vs EU-Prolia	AUCinf (day*ng/mL)	366000	247	369000	246	0.99	(0.93, 1.05)
	Cmax (ng/mL)	6910	260	7120	258	0.97	(0.92, 1.03)

n = number of subjects with evaluable PK parameters
An ANCOVA was performed on log-transformed PK parameters including treatment as fixed factor and weight as continuous covariate.

Drug serum concentrations

Drug serum concentration time profiles after the first dose are shown in the following figure.

Figure 4. Drug concentrations – time profile, TP1 (PKS)



A lower SD whisker is not displayed if mean-SD<0 since this is biologically implausible.

Summary statistics of PK parameters

Summary statistics of PK parameters after the first dose are provided in the tables below.

Table 13. summary statistics for PK parameters, TP1 – PKS

Parameter	Statistics	GP2411 N=260	Prolia N=258
AUCinf (day*ng/mL)	n	247	246
	Mean (SD)	407000 (173000)	398000 (175000)
	CV%	42.5	44.0
	Geo-mean	370000	365000
	Geo-CV%	47.8	43.3
	Median	399000	364000
	Min-Max	85200-1120000	94200-1380000
AUClast (day*ng/mL)	n	260	258
	Mean (SD)	394000 (173000)	385000 (176000)
	CV%	44.0	45.6
	Geo-mean	355000	348000
	Geo-CV%	51.5	48.7
	Median	376000	353000
	Min-Max	77400-1110000	51800-1340000
AUC % extrap (%)	n	247	246
	Mean (SD)	1.02 (1.90)	0.850 (1.99)
	CV%	185.7	234.4
	Geo-mean	0.399	0.351
	Geo-CV%	264.6	230.0
	Median	0.462	0.428
	Min-Max	0.0112-20.2	0.0170-26.4
Cmax (ng/mL)	n	260	258
	Mean (SD)	7640 (3290)	7700 (3320)
	CV%	43.1	43.1
	Geo-mean	6970	7050
	Geo-CV%	45.8	44.2
	Median	7290	6940
	Min-Max	1810-20700	1820-20100
Lambda z (1/day)	n	247	246
	Mean (SD)	0.0450 (0.0173)	0.0453 (0.0163)
	CV%	38.4	36.1
	Geo-mean	0.0416	0.0424
	Geo-CV%	42.8	39.1
	Median	0.0425	0.0432
	Min-Max	0.0118-0.0870	0.00789-0.110
T1/2 (day)	n	247	246
	Mean (SD)	18.2 (8.49)	17.7 (8.06)
	CV%	46.6	45.6
	Geo-mean	16.7	16.4
	Geo-CV%	42.8	39.1
	Median	16.3	16.0
	Min-Max	7.97-58.7	6.33-87.9

CV% = coefficient of variation (%)=sd/mean*100; Geo-CV% = (sqrt (exp (variance for log transformed data)-1))*100

Summary statistics for Tmax, TP1
PKS

Parameter	Statistics	GP2411 N=260	Prolia N=258
Tmax (day)	n	260	258
	Median	13.0	9.94
	Min-Max	2.87-56.0	2.79-159

2.6.2.2. Pharmacodynamics

Analytical Methods

PD assay:

The assay to quantify CTX-I in human serum from HV and patients with PMO was validated in line with guideline EMEA/CHMP/EWP/192217/2009 on bioanalytical method validation. All validation parameters passed the acceptance criteria.

Taken together, the assay for quantification of CTX-I is considered suitable for its intended use. Performance of the assay during clinical studies 101 and 301 is considered acceptable.

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 CGP24112101

For a detailed assessment of the design of study CGP24112101 please refer to section 2.6.2.1 Pharmacokinetics. Only PD specific aspects of this study are provided below.

Pharmacodynamic data analysis

Serum samples will be analysed for CTX and PINP concentrations. PD parameters of CTX only, following a single s.c. dose of 35 mg study medication will be estimated using the noncompartmental drug effect model in Phoenix WinNonlin (Version 8.0 or above) by the pharmacokineticist of a CRO. For the determination of PD similarity, the area under the effect versus time curve (AUEC) of baseline corrected serum CTX concentrations (% change from baseline) will be the secondary parameter of interest. The AUEC will be calculated as the area below 0 after the 35 mg s.c. dose until CTX values return and cross 0 for the first time. For subjects where CTX does not cross or even return to baseline, the data up to 39 weeks will be used in the calculation.

In addition to the AUEC calculation as described above, the rebound area, where applicable, will be calculated as an additional PD parameter. The PD parameters together with the abbreviations and definitions are provided in the table below.

Table 14. PD parameters for CTX

Parameter	Description
AUEC	The area that is below 0 and above the response curve [% x day] until CTX values return and cross the baseline for the first time. For subjects where CTX does not cross or even return to baseline, the AUEC of up to 39 weeks will be calculated.
Rebound area	The area that is above 0 and below the response in terms of %CfB in CTX curve [% x day] from the first time %CfB in CTX values return and cross 0 up to 39 weeks. Considering that 0 may be crossed more than once (oscillation), the rebound area is defined as the sum of all areas above 0. If %CfB in CTX does not return to 0 from Day 1 to Week 39 then the rebound area will be defined as zero.

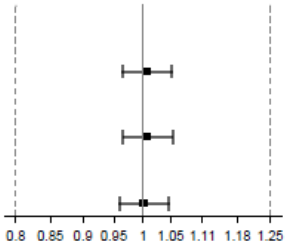
Pharmacodynamic results

AUEC of %CfB in serum CTX

The 95% Cis for the ratios (GP2411/Xgeva-EU, GP2411/Xgeva-US and Xgeva-EU/Xgeva-US) of geometric means for AUEC of %CfB in serum CTX are provided in the figure below.

Table 15. Geometric mean ratio and 95% CI for AUEC of %CfB in CTZ to compare treatments (PDS)

Treatment Comparison	Parameter	n1 (Test)	n2 (Reference)	Point Estimate	95% CI Lower	95% CI Upper	Forest Plot
GP2411 vs Xgeva-EU	Area Under the Effect Curve (%*day)	161	166	1.01	0.96	1.05	
GP2411 vs Xgeva-US	Area Under the Effect Curve (%*day)	161	161	1.01	0.97	1.05	
Xgeva-EU vs Xgeva-US	Area Under the Effect Curve (%*day)	166	161	1.00	0.96	1.05	

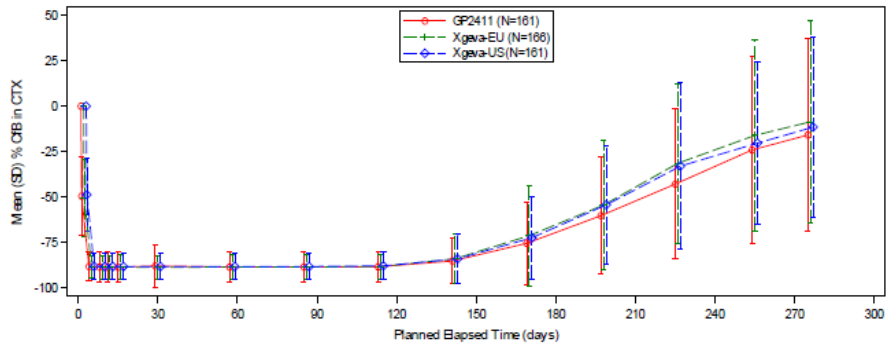


Fitting ANCOVA model to log of AUEC of %CfB in CTX as dependent variable with treatment and vitamin D replenishment as factors and log of baseline CTX as a covariate.
The dashed vertical lines indicate the equivalence margins of 0.80 and 1.25.

CTX serum concentrations

The profiles of %CfB in CTX serum concentrations were similar for all treatment groups (see figure below).

Figure 5. %CfB in CTX – time profile (PDS)

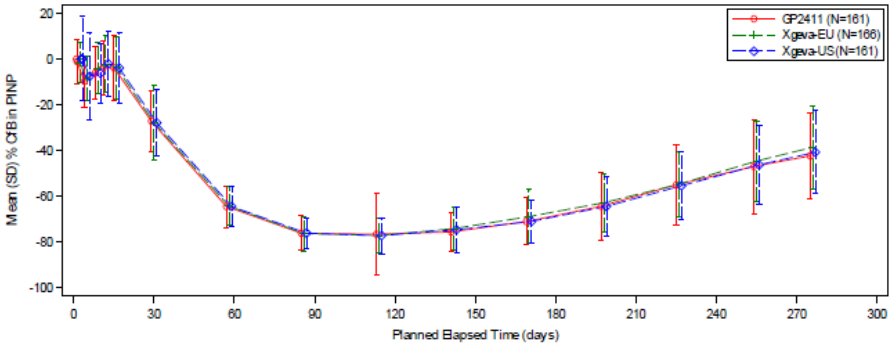


A lower SD whisker is not displayed if mean-SD<-100% since this is biologically implausible.

PINP serum concentrations

The profiles of %CfB in PINP serum concentrations were similar in the treatment groups (see figure below).

Figure 6. %CfB in PINP – time profile (PDS)



A lower SD whisker is not displayed if mean-SD<-100% since this is biologically implausible.

Summary statistics of PD parameters

Summary statistics of AUEC %CfB in serum CTX were in general similar across all treatment groups (see table below). Summary statistics of the rebound area for %CfB in serum CTX are available in the table below. The rebound effect occurs after discontinuation of denosumab. Serum CTX values crossed the baseline (i.e. %CfB >0) for less than 40% of subjects.

Table 16. Summary statistics for PD parameters – PDS

Parameter	Statistics	GP2411 N=161	Xgeva-EU N=166	Xgeva-US N=161
Area Under the Effect Curve (%*day)	n	161	166	161
	Mean (SD)	19600 (3740)	19200 (3350)	19100 (3330)
	CV%	19.1	17.5	17.4
	Geo-mean	19100	18800	18800
	Geo-CV%	28.2	18.9	19.0
	Median	20400	20000	19500
	Min-Max	1830-25500	10400-25300	9540-24900
Rebound area (%*day)	n	161	166	161
	n of > 0	49	63	61
	Mean (SD)	522 (2110)	793 (2170)	566 (1680)
	CV%	404.5	273.1	296.8
	Geo-mean	313	464	291
	Geo-CV%	1449.9	1486.7	1459.6
	Median	0.00	0.00	0.00
	Min-Max	0.00-22700	0.00-16500	0.00-12000

n = number of subjects with non-missing PD parameters.
CV% = coefficient of variation (%)=sd/mean*100; Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100
Geo-mean is only calculated for parameter values >0.

Sensitivity analysis

A sensitivity analysis of the secondary PD endpoint AUEC %CfB of serum CTX was performed excluding the 35 subjects which were enrolled before the COVID-19 pandemic (defined as before 01-March-2020). These subjects were also those subjects who did not have to take any vitamin D and calcium supplementation because they were enrolled before introduction of supplementation with Protocol Amendment 3.

The results of the sensitivity analysis are provided in the table below.

Table 17. Geometric mean ratio (Test/Reference) and 95% confidence intervals for AUEC of % CfB in CTZ excluding pre-pandemic subjects – PDS

		Adjusted Geo-Mean				Geo-Mean Ratio Test/Reference		
Test vs Reference (Comparison)	Parameter (unit)	Test	n	Reference	n	Point Estimate	CV%	(95% CI)
GP2411 vs Xgeva-EU	Area Under the Effect Curve (%*day)	18900	151	18800	155	1.01	20.5	(0.96, 1.05)
GP2411 vs Xgeva-US	Area Under the Effect Curve (%*day)	18900	151	18800	147	1.00	20.5	(0.96, 1.05)
Xgeva-EU vs Xgeva-US	Area Under the Effect Curve (%*day)	18800	155	18800	147	1.00	20.5	(0.95, 1.04)

n = number of subjects with evaluable parameters in each treatment group.
CV% = sqrt (exp (residual variance from ANCOVA)-1)*100
Fitting ANCOVA model to log of AUEC of % CfB in CTX as dependent variable with treatment and vitamin D replenishment as factors and log of baseline CTX as a covariate. The similarity margins are set to 0.80 and 1.25.
Pre-pandemic subjects are subjects enrolled prior to 01-Mar-2020.

Study CGP24112301

For a detailed assessment of the design of study CGP24112301 please refer to section 2.6.5 "Clinical Efficacy". Only PD specific aspects of this study are provided below.

Pharmacodynamic data analysis

Serum samples will be analyzed for CTX and PINP concentrations. PD parameters of baseline corrected serum CTX concentrations only (% change from baseline) following the first s.c. dose of 60 mg study drug will be estimated in a blinded manner using the non-compartmental drug effect model in Phoenix WinNonlin (Certara, Version 8.0 or above) by the pharmacokineticist of a CRO and reviewed by the Sandoz PK expert. The PD parameters together with the abbreviations and definitions are provided in the table below.

Table 18. PD parameters for CTX

Parameter	Description
AUEC	The area that is below 0 and above the response curve [% x day] until CTX values return and cross the baseline for the first time. For patients where CTX does not cross or even return to baseline, the AUEC of up to 26 weeks will be calculated.
Rebound area	The area that is above 0 and below the response in terms of %CfB in CTX curve [% x day] from the first time %CfB in CTX values return and cross 0 up to 26 weeks. Considering that 0 may be crossed more than once (oscillation), the rebound area is defined as the sum of all areas above 0. If %CfB in CTX does not return to 0 from Day 1 to Week 26 then the rebound area will be defined as zero.

Pharmacodynamic results

Primary PD analysis

AUEC of %CfB in serum CTX after the first dose: ratio with 95% CI

The AUEC of %CfB in serum CTX was assessed after the first dose. The results of the primary PD analysis are provided in the table below.

Table 19. Geometric mean ratio (GP2411/EU-Prolia) and 95% CI for AUEC of %CfB in CTX after first dose (PDS)

		Adjusted Geo-Mean		Geo-Mean Ratio Test/Reference	
Test vs Reference (Comparison)	Parameter (unit)	GP2411 (N=228)	EU-Prolia (N=213)	Point Estimate	(95% CI)
GP2411 vs EU-Prolia	Area Under the Effect Curve (%*day)	15800	15800	1.00	(0.98, 1.01)

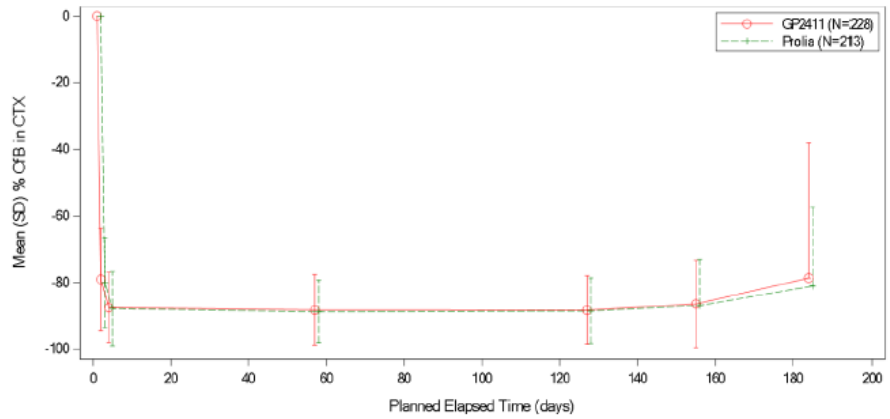
An ANCOVA was performed on log-transformed AUEC of %CfB in CTX after first dose including treatment as fixed factor and log-transformed baseline CTX as continuous covariate.

Secondary PD endpoints

CTX serum concentrations

The %CfB in CTX time profile after the first dose is shown in the figure below.

Figure 7. Percentage in CfB in CTX – time profile after the first dose (PDS)

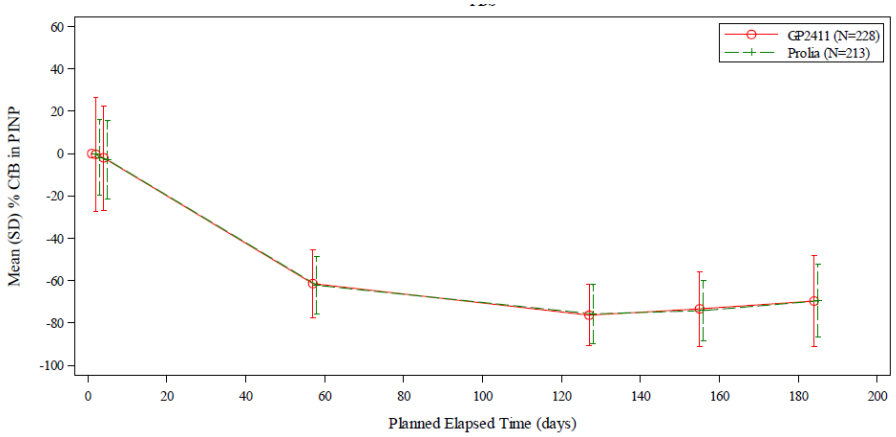


A lower SD whisker is not displayed if mean-SD<-100% since this is biologically implausible.

PINP serum concentrations

The %CfB in PINP time profile after the first dose is shown in the figure below.

Figure 8. Percentage in CfB in PINP – time profile, TP1 (PDS)



Additional PD parameters

Summary statistics of the CTX rebound area after first dose are presented in the table below.

Table 20. Summary statistics for PD parameters, TP1 (PDS)

Parameter	Statistics	GP2411 N=228	Prolia N=213
Area Under the Effect Curve (%*day)	n	228	213
	Mean (SD)	15900 (2010)	16000 (1830)
	CV%	12.7	11.4
	Geo-mean	15700	15900
	Geo-CV%	15.8	14.0
	Median	16600	16500
	Min-Max	6440-19000	5930-18900
Rebound area (%*day)	n	228	213
	n of >0	3	4
	Mean (SD)	28.2 (384)	12.6 (122)
	CV%	1363.4	962.4
	Geo-mean	716	157
	Geo-CV%	664.3	13870.0
	Median	0.00	0.00
	Min-Max	0.00-5780	0.00-1510

CV% = coefficient of variation (%)=sd/mean*100; Geo-CV% = (sqrt (exp (variance for log transformed data)-1))*100

PD sensitivity analysis

A post-hoc analysis was conducted to investigate the impact of the high number of exclusions (86 subjects) from the PD analyses. The reasons leading to exclusion from the modified PD analysis set are summarized in the following table.

Table 21. Sensitivity analysis: exclusion from modified PDS (TP1 RAS)

	GP2411 N=263 n (%)	EU-Prolia N=264 n (%)
Total exclusions	7 (2.7)	14 (5.3)
Protocol deviations leading to exclusion from PDS	0	1 (0.4)
Other reasons for exclusion from PDS (AUEC value missing or excluded from analysis)	7 (2.7)	14 (5.3)
Pre-dose sample at visit 2 not taken prior treatment	4 (1.5)	1 (0.4)
Pre-dose visit 2 result < 24% above LLOQ	3 (1.1)	10 (3.8)
Visit 2 pre-dose PK result above LLOQ	0	5 (1.9)

The results from this post-hoc analysis are presented in the following table.

Table 22. Geometric mean ratio (GP2411/EU-Prolia) and 95% CI for AUEC of %CfB in CTZ after first dose (modified PDS)

		Adjusted Geo-Mean		Geo-Mean Ratio Test/Reference	
Test vs Reference (Comparison)	Parameter (unit)	GP2411 (N=256)	EU-Prolia (N=250)	Point Estimate	(95% CI)
GP2411 vs EU-Prolia	Area Under the Effect Curve (%*day)	15100	15500	0.98	(0.93, 1.02)

An ANCOVA was performed on log-transformed AUEC of %CfB in CTX after first dose including treatment as fixed factor and log-transformed baseline CTX as continuous covariate.

2.6.3. Discussion on clinical pharmacology

The clinical development program of GP2411 included two studies to demonstrate PK and PD similarity between denosumab biosimilar GP2411 and the reference products.

Study CGP24112101 was a randomized, double-blind, three-arm, parallel group, single dose study in healthy male subjects to demonstrate similarity in PK, PD, safety and immunogenicity between GP2411, EU-authorized Xgeva and US-licensed Xgeva. The study was conducted at two investigational sites in Germany. Subjects were randomized in a 1:1:1 ratio. After the screening period (up to 5 weeks), subjects received one single dose of 35 mg s.c. of GP2411, EU-authorized Xgeva or US-licensed Xgeva. The follow-up period was 39 weeks. Due to the long half-life of denosumab (mean half-life 28 days), a parallel design rather than a cross-over design was chosen. This is considered appropriate. Overall, the design of study CGP24112101 is acceptable and has been discussed in several EMA Scientific Advice procedures (EMEA/H/SA/3409/1/2016/III, EMEA/H/SA/3409/2/2017/III, EMEA/H/SA/3409/2/FU/1/2018/III and EMA/SA/0000067538). Generally, the design is aligned with the advice received.

The study started on 27-Jan-2020 with the first subject signing informed consent and was completed on 09-Jun-2022 with the last subject last assessment. Due to the COVID-19 pandemic, the screening and randomization was paused from 16-Mar-2020 to 23-Jul-2020. The database lock was on 19-Jul-2022. However, the clinical database had to be unlocked to correct treatment information for 2 subjects and to document an important protocol deviation in the eCRF (use of prohibited medication that could influence the bone metabolism). After the update of the clinical database, it was re-locked on 08-Aug-2022. The Applicant was asked to provide more information on this unlocking of the clinical database. The Applicant provided the requested information on the unlocking and re-locking of the clinical database. Regarding the incorrect study treatment, the applicant clarified that all study participants received the correct study treatment, but the transcription of the data from the source document to the eCRF page was incorrect for two subjects and this erroneous information was only identified upon unblinding of the database. This explanation is acceptable. Regarding the non-availability of the information on the use of prohibited medication with impact on bone metabolism, the applicant clarified that this information has already been available in the database before the initial database lock, but it was erroneously not documented as important protocol deviation on the respective eCRF page. According to the applicant, this was due to human error. The explanation provided by the applicant can be followed and no further concern arises.

The protocol of the study was amended five times. The Applicant provided a detailed overview of the protocol amendments and provided all relevant protocol versions. No concerns arise from the amendments.

For study CGP24112101, a healthy male subject population was recruited. The main inclusion criteria were age between 28-65 years, body weight between 50.0 and 90.0 kg and BMI between 18.5 and 29.9 kg/m2. The conduct of the study only in male subjects is endorsed, as this represents a homogenous and sensitive model to demonstrate, or exclude, differences between the treatment arms, if existent. The body weight range restrictions are also appropriate to lower PK variability. The exclusion criteria were chosen to recruit a healthy subject population without prior exposure to denosumab or any other medication used for the treatment of osteoporosis, or otherwise having an influence on bone metabolism. This is endorsed. Vitamin D deficiency was one of the exclusion criteria. However, there was the possibility for a single attempt to replenish Vitamin D levels and re-evaluate this criterion before randomization. This is considered acceptable. There was also a re-evaluation of other exclusion criteria at the day-1 visit, which is acceptable. At the day-1 visit, an additional exclusion criterion was "Positive result for a test for SARS-CoV-2, performed at site at Day −1 (Visit 2). This could be through a RT-PCR test or an alternative test with comparable sensitivity and

specificity.”. This is endorsed. Overall, the inclusion and exclusion criteria are considered appropriate for the recruitment of a healthy male subject population.

A single dose of GP2411, EU sourced Xgeva and US sourced Xgeva was administered subcutaneously at day 1. The route of administration is in line with the recommendations of the Xgeva SmPC and therefore acceptable. The chosen dose for the study in healthy volunteers was 35 mg and is therefore lower than the recommended dose from the Xgeva SmPC. The sub-therapeutic dose of 35 mg has been discussed in previous EMA Scientific Advice (EMEA/H/SA/3409/1/2016/III, EMEA/H/SA/3409/2/2017/III, EMEA/H/SA/3409/2/FU/1/2018/III and EMA/SA/0000067538) and was regarded acceptable in combination with the study duration of 39 weeks and Study 301 being conducted with the 60 mg dose in the PMO patient population (entire PK profile captured, target and non-target-mediated clearance mechanism addressed, return of CTX to baseline covered). It is agreed with the applicant that the dose of 35 mg is considered sensitive to detect differences regarding PK and PD among the treatment arms and is therefore considered appropriate for this study. Additionally, after protocol amendment 3, all enrolled subjects received calcium (1000 mg/day) and vitamin D (400 IU/day) supplementation which had to be taken from Day −7 up to Day 28. According to the SmPC of Xgeva, the supplementation with calcium and vitamin D is required in all patients. Thus, the applicant was asked to explain why this additional study treatment has only been introduced after protocol amendment 3 and was not mandatory from the very beginning of the study. The Applicant outlined that the decision was based on a benefit-risk balance where it was considered that the risk of hypocalcaemia in healthy volunteers is low with a single sub-therapeutic dose of 35 mg. However, after the start of the study, the supplementation with protocol amendment 3 was introduced, which was accepted by CHMP.

Of note, the applicant provided a sensitivity analysis for the primary PK parameters excluding the 35 subjects enrolled before the COVID-19 pandemic. The excluded subjects were also those subjects who did not take any vitamin D and calcium supplementation because they were enrolled before introduction of supplementation with Protocol Amendment 3. Thus, no further analyses regarding subjects with supplementation of calcium/vitamin D will be requested.

The primary objective of Study CGP24112101 was the demonstration of PK similarity among GP2411, Xgeva-EU and Xgeva-US. The secondary objectives included safety, immunogenicity and PD aspects of GP2411 and the reference products. This is overall endorsed.

The primary PK endpoints in Study CGP24112101 were AUCinf, AUClast and Cmax after a single s.c. dose of 35 mg denosumab. According to the “Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)”, in case of subcutaneous administration, AUCinf and Cmax should be evaluated as co-primary parameters. AUClast was added as additional co-primary endpoint after discussion with the FDA. The choice of the primary endpoints is considered adequate. The secondary PD endpoints “AUEC of %CfB in serum CTX” and “serum concentrations of CTX and PINP per visit” are also considered acceptable for the demonstration of PD similarity of GP2411, Xgeva-EU and Xgeva-US. There were no secondary PK endpoints defined in the study protocol. However, the applicant has pre-defined the analysis of additional PK parameters, such as Tmax, Lambda_z, AUC%extrap and T1/2 in the SAP, which is considered adequate.

Subjects were randomized in a 1:1:1 ratio to one of the three treatments groups. The process of randomization was adequately described and is considered acceptable.

Study CGP24112101 was a double-blind study. The study was subject- and investigator-blinded. As the appearance of the GP2411 and Xgeva vials differs, the pharmacy/site staff who prepared the syringes for s.c.

administration was unblinded but was not involved in any further study assessments. The treatment remained blinded to the subjects and to the study personnel administering the dose, as the same type of syringe was used for the s.c. administration of Xgeva and GP2411. This is endorsed. The process of blinding was adequately described and is considered acceptable.

The PK parameters in study CGP24112101'were calculated by non-compartmental analysis methods using Phoenix WinNonlin® version 8.0 or above. This is considered acceptable.

The definitions of the analysis sets are considered adequate.

Concerning statistical methodology, the use of an ANCOVA for primary efficacy evaluation of the PK parameters Cmax, AUClast and AUCinf is supported. However, the stratification variable, vitamin D replenishment, was omitted in the model although it is recommended to include all stratification variables in the analysis according to the EMA Guideline on adjustment for baseline covariates in clinical trials. The Applicant explained their rationale for this deviation from the guideline, but anyway for impact assessment of this deviation, an ANCOVA model including also vitamin D was fitted by the Rapporteur based on submitted raw data, and resulting confidence intervals were well included in the equivalence margin. Therefore, no concern arises.

PD similarity with the endpoint AUEC of %CfB in serum CTX concentrations was assessed as secondary analysis in terms of an 95% confidence interval retrieved from an ANCOVA model, which is endorsed. Although justified, the ANCOVA model did not include weight, which was a stratification factor at randomisation. Therefore, the analysis was conducted by the Rapporteur based on submitted raw data with weight additionally included in the model, which showed that the inclusion did not alter the conclusion of the secondary endpoint results.

Overall, the participant flow is described in sufficient detail and is comprehensible. Of the 1137 screened subjects, 502 subjects were randomized in a 1:1:1 ratio. Non-randomization (635 subjects) was due to screen failure (505 subjects), physician decision (49 subjects), subject decision (77 subjects), adverse event (2 subjects) and technical problems (2 subjects). Of the 502 randomized subjects, 492 completed the study. The reasons for discontinuation were adverse event (1 subject in the GP2411 group), lost to follow-up (2 subjects in the GP2411 group), physician decision (1 subject in the GP2411 group and 1 subject in the Xgeva-US group), randomized by mistake without study treatment (1 subject in the Xgeva-US group) and subject decision (2 subjects in the GP2411 group and 2 subjects in the Xgeva-US group). Thus, the number of subjects completing the study was high. Furthermore, the number of subjects discontinuing the study was similar among groups.

The number of subjects with at least one important protocol deviation was 180. There were more subjects in the Xgeva-EU group (73 subjects) having a protocol deviation than in the GP2411 (53 subjects) and Xgeva-US (54 subjects) groups. The reason for the higher number of protocol deviations in the Xgeva-EU group is unclear and no obvious explanation for this is available. The Applicant was asked to provide a possible explanation. The Applicant outlined why from their point of view the higher number of protocol deviations in the Xgeva-EU group might be a chance finding. A table summarizing the protocol deviations from this study was provided. It is agreed to the applicant that the observed increase in the number of protocol deviations in the Xgeva-EU group might be due to an additive effect of small increases in several protocol deviations. The explanation provided by the applicant is thus regarded acceptable. The most common protocol deviation among all groups was "study visit performed outside of allowed time window", followed by "PD sampling not performed between 7:30 and 10:00 am" and "missed study visit". The protocol deviations "study visit performed outside of allowed time window" and "missed study visit" might to some extent be explainable by

the COVID-19 pandemic. Regarding the protocol deviation "PD sampling not performed between 7:30 and 10:00 am", this criterion was introduced as a measure to standardise the sampling time and reduce variability. In the SAP it is stated that "if the larger sampling time window from 7:00-11:00 am or the fasting status were violated, the respective CTX sample will be flagged and listed but excluded from the derivation of AUEC %CFB". Nevertheless, these subjects do not seem to have been excluded from the PDS analysis set, as the number of subjects excluded from this set was 5 for the GP2411 group, 5 for the Xgeva-EU group and 4 for the Xgeva-US group (see section "Numbers analysed" further below), and therefore lower than subjects having the protocol deviation "PD sampling not performed between 7:30 and 10:00 am". Thus, the applicant was asked to provide more details on the subjects having PD sampling performed outside the 7:30 and 10:00 am time window and possible implications on PD results. From the 40 subjects with a time window deviation, most of the subjects only had one time window deviation and only five subjects had two time window deviations. The Applicant provided a table with the frequency of PD sampling performed outside the 7:30 and 10:00 am time window, the median and range of time deviation from this time window by treatment arm and per study visit and overall. It is agreed to the applicant that based on the sample level, the frequency of deviations is low (0.8% of 2436 GP2411 samples, 0.7% of 2549 Xgeva-EU samples and 0.3% of 2409 Xgeva-US samples). The median time deviations from the allowed time window was 7 min for the GP2411 samples, 9.5 min for the Xgeva-EU samples and 10 min for the Xgeva-US samples. Regarding possible implications on PD results, the applicant provided an analysis of AUEC after excluding subjects with time window deviations. This analysis confirmed the results seen with the pre-specified PD analysis set. In conclusion, the applicant provided the requested information and no further concern arises.

The baseline characteristics were well balanced among the GP2411, Xgeva-EU and Xgeva-US groups. The mean age was 47.0, 44.5 and 46.0 years, respectively. Most of the subjects in the study were "White" (98.4%) and "Not Hispanic or Latino" (99.0%). The race and ethnicity aspects were well balanced among the groups. In addition, the height and weight of the subjects was comparable among the groups and a similar number of subjects had Vitamin D replenishment among the groups. Thus, the demographics data show that a very homogeneous population of healthy male subjects was recruited that is considered sensitive to elucidate differences between GP2411 and the reference products, if existent. The applicant also provided an overview of the medical history, concurrent conditions and prior/concomitant medication. Overall, these aspects showed a similar pattern across treatment groups and no concerns arise from these data.

The Applicant provided an overview of the number of subjects per analysis set. The number of subjects randomized to the study was 502 (RAS set). In the SAF set, three subjects were missing in the Xgeva-US group, due to not receiving study treatment. Nine subjects were excluded from the PKS set and 14 subjects were excluded from the PDS set with similar numbers among treatment groups. The reasons for exclusion from the PKS and PDS sets were provided and were according to the definition in the study protocol/SAP. The most common reason for exclusion from the PKS set was "Cmax, AUCinf and AUClast are missing or excluded from analysis" and the most common reason for exclusion from the PDS set was "AUEC value missing or excluded from analysis". The numbers analysed were well presented by the applicant and are considered appropriate.

The primary PK endpoints of Study CGP24112101 were met. The point estimate of the ratio (GP2411/Xgeva-EU) of the geometric mean for AUCinf was 1.09 with the corresponding 90% CI being (1.03; 1.16). The point estimate of the ratio (GP2411/Xgeva-EU) of the geometric mean for AUClast was 1.08 with the corresponding 90% CI being (1.01; 1.14). The point estimate of the ratio (GP2411/Xgeva-EU) of the geometric mean for Cmax was 1.02 with the corresponding 90% CI being (0.97; 1.08). Thus, all PK parameters of the GP2411/Xgeva-EU comparison were within the pre-specified equivalence criteria for these primary PK analyses.

The Applicant provided the mean drug serum concentrations time-profile. The profiles were comparable among the GP2411, Xgeva-EU and Xgeva-US groups. The Applicant also provided the individual drug serum concentrations with the scheduled an actual sampling time point for each subject. This is acknowledged. However, the applicant is also asked to provide the individual serum concentration time-profiles for each subject separately. The individual serum concentration time-profiles have already been plotted by the Rapporteur based on submitted raw data. No follow up questions arise.

The summary statistics of the PK parameters revealed that the PK parameters AUCinf, AUClast, Cmax, T1/2, AUC%extrap, Lambda_z and Tmax were similar among the three treatment groups GP2411, Xgeva-EU and Xgeva-US. Thus, these data support the PK similarity of the test and reference products.

A sensitivity analysis for the primary PK parameters excluding the subjects enrolled before the COVID-19 pandemic was provided. The results of this analysis are similar to the results of the primary analysis. The excluded subjects were also those subjects who did not have to take any vitamin D and calcium supplementation because they were enrolled before introduction of supplementation with Protocol Amendment 3.

The Applicant provided data on the influence of post anti-drug antibodies and pharmacokinetics. The AUCinf, AUClast and Cmax were similar in ADA-positive and ADA-negative subjects, across all treatment groups. Thus, there seems to be no impact of ADAs on the PK of GP2411, EU-Xgeva or US-Xgeva. This is endorsed.

The PD parameters in study CGP24112101 were calculated by non-compartmental drug effect model using Phoenix WinNonlin® version 8.0 or above. For the determination of PD similarity, the area under the effect versus time curve (AUEC) of baseline corrected serum CTX concentrations (% change from baseline) will be the secondary parameter of interest. The AUEC was calculated as the area below 0 until CTX values return and cross 0 for the first time. Additionally, the rebound area was calculated if applicable. This is considered acceptable. For the calculations of the AUEC and the rebound area, the applicant provided detailed definitions. For the AUEC, the area that is below 0 and above the response curve until CTX values cross the baseline for the first time was calculated. For the rebound area, the sum of all areas above 0 and below the response curve was calculated. Thus, while for the AUEC the area until the response curve crosses 0 for the first time was calculated, for the rebound area the sum of all areas above 0 was calculated.

Of note, based on the submitted raw data, the Rapporteur has already calculated AUEC with an alternative definition (sum of all areas below 0). The results are very similar to the results with the original AUEC definition.

In study CGP24112101, the "AUEC of %CfB in serum CTX" was evaluated as a secondary endpoint. The point estimate of the geometric mean ratio (GP2411/Xgeva-EU) for AUEC was 1.01 with the corresponding 95% CI being (0.96; 1.05). Thus, the 95% CI for the ratio of geometric mean for AUEC of %CfB in serum CTX was within the pre-specified acceptance criteria of 0.8 to 1.25, which supports PD similarity of the test and reference product.

The Applicant also provided the mean %CfB in CTX serum concentration profile over time. Overall, the profiles were comparable across the GP2411, Xgeva-EU and Xgeva-US groups. In addition, the applicant provided the summary statistics of CTX serum concentration for each timepoint. Overall, the levels of CTX were comparable among the treatment groups at each timepoint and also the percent change from baseline was similar among the groups at each timepoint. Thus, the results support the PD similarity of the test and reference products.

The Applicant also provided the mean %CfB in PINP serum concentration profile over time. Overall, the profiles were comparable across the GP2411, Xgeva-EU and Xgeva-US groups. In addition, the summary statistics of PINP serum concentration for each timepoint were presented. Overall, the levels of PINP were suppressed

similarly among the treatment groups at each timepoint post-dose and the percent change from baseline was also similar among the groups at each timepoint. Thus, these results support the PD similarity of the test and reference products.

The AUEC %CfB in serum CTX was 19600 %*day, 19200 %*day and 19100 %*day for the GP2411, Xgeva-EU and Xgeva-US group, respectively. Thus, the levels were similar across the treatment groups. The rebound area (area under the response curve that is above 0) was also investigated as a pharmacodynamic parameter in this study. The mean rebound area was 522 %*day, 793 %*day and 566 %*day for the GP2411, Xgeva-EU and Xgeva-US group, respectively. The serum CTX values crossed the baseline in only 49 subjects of the GP2411 group, 63 subjects of the Xgeva-EU group and 61 subjects of the Xgeva-US group. Thus, due to the high variability and the low number of subjects crossing baseline these results are difficult to interpret. Therefore, the rebound area does not seem to be a very sensitive parameter to be used in the overall similarity setting.

Study CGP24112301 was a randomized, double-blind, multicentre, integrated phase I/III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity of GP2411 and EU-authorized Prolia.

For the analysis of PK similarity between GP2411 and EU-Prolia in osteoporosis patients, the applicant provided the geometric mean ratios of the PK parameters AUCinf and Cmax. The point estimate of the ratio (GP2411/EU-Prolia) of the geometric mean for AUCinf was 0.99 with the corresponding 90% CI being (0.93; 1.05). The point estimate of the ratio (GP2411/EU-Prolia) of the geometric mean for Cmax was 0.97 with the corresponding 90% CI being (0.92; 1.03). Thus, after the first dose in patients, the PK parameters AUCinf and Cmax were similar between the GP2411 and the EU-Prolia group. This is endorsed.

In addition, the applicant provided the mean drug serum concentration time profiles after the first dose in patients. The profiles were similar for the GP2411 and EU-Prolia group, which is acknowledged. The Applicant also provided the drug serum concentrations as per visit schedule up to Week 78, which showed that the mean serum concentrations were similar between the groups for each visit. In addition, the applicant also provided the individual drug serum concentrations with the scheduled an actual sampling time point for each subject up to week 78. This is acknowledged.

The summary statistics of PK parameters revealed that the mean AUCinf, mean AUClast mean Cmax, lambda_z and AUC%extrap and T1/2 were similar between the GP2411 and EU-Prolia group. The median Tmax was 13.0 days for the GP2411 group and 9.94 days for the EU-Prolia group. Thus, the Tmax was quite different between the groups. While the Tmax in the EU-Prolia group was similar to what has been observed in study CGP24112101, the Tmax in the GP2411 group of study CGP24112301 was divergent. Due to the less frequent sampling around Cmax in study CGP24112301, Tmax might not have been sensitively assessed in this study. Therefore, no question on the numerical difference is raised.

Moreover, the applicant provided data on the influence of post anti-drug antibodies on pharmacokinetics. The results of these analyses suggest that there is no impact of ADAs on the PK of GP2411 or EU-Prolia. This is endorsed.

The PD parameters in Study CGP24112301 were calculated by non-compartmental drug effect model using Phoenix WinNonlin® version 8.0 or higher. The AUEC was calculated as the area below 0 until CTX values return and cross 0 for the first time. Additionally, the rebound area was calculated if applicable. This is considered acceptable. Due to the very low number of patients returning to CTX baseline after the first dose, an alternative definition of AUEC and rebound area, is not regarded necessary for study CGP24112301.

The adjusted geometric-mean for the AUEC of %CfB in CTX was 15800%*day for the GP2411 group and 15800%*day for the EU-Prolia group. The point estimate of the ratio (GP2411/EU-Prolia) of the geometric mean for AUEC of %CfB in CTX after the first dose was 1.00 with the corresponding 95% CI being [0.98; 1.01]. Thus, the primary PD endpoint was met, as the 95% CI was within the pre-specified equivalence criteria of [0.8, 1.25]. This is endorsed.

Of note, the results of the co-primary endpoint "Percent change from baseline in LS-BMD at Week 52" are discussed further below in the Clinical efficacy section.

The Applicant provided the mean %CfB in CTX serum concentration time profile. Overall, the profiles were comparable between the GP2411 and the EU-Prolia group. The Applicant also provided the summary statistics of CTX serum concentration for each timepoint. Overall, the levels of CTX and corresponding percent change from baseline were comparable between the treatment groups at each timepoint. Thus, the results support the PD similarity of the test and reference product.

The Applicant provided the mean %CfB in PINP serum concentration time profile. Overall, the profiles were comparable between the GP2411 and the EU-Prolia group. The Applicant also provided the summary statistics of PINP serum concentration for each timepoint. Overall, the levels of PINP and corresponding percent change from baseline were comparable between the treatment groups at each timepoint. Thus, the results support the PD similarity of the test and reference product.

The AUEC %CfB in serum CTX was 15900 %*day and 16000 %*day for the GP2411 and EU-Prolia group, respectively. Thus, the levels were similar across the treatment groups. The rebound area (area under the response curve that is above 0) was also investigated as a pharmacodynamic parameter in this study. The mean rebound area was 28.2 %*day and 12.6 %*day for the GP2411and EU-Prolia group, respectively. As the serum CTX values crossed the baseline in only 3 subjects of the GP2411 group and 4 subjects of the EU-Prolia group, these results are difficult to interpret and do not provide further insights into the PD similarity of the test and reference product.

The Applicant provided a post-hoc analysis to account for the high number of subjects excluded from the PDS set. The results of the analysis with the modified PD set (less exclusions) support the results of the primary PD analysis. This is acknowledged.

2.6.4. Conclusions on clinical pharmacology

Overall, the design of the study CGP24112101 was appropriate and mostly in line with previous EMA Scientific Advice received. The primary PK endpoints of the study were met and the applicant could demonstrate comparable PK between GP2411, EU-authorized Xgeva and US-licensed Xgeva. Regarding PD, "AUEC of %CfB in serum CTX" was evaluated as a secondary endpoint and supported similarity of the test and reference product. These results were supported by comparable %CfB in CTX/PINP time-profiles among the treatment groups.

The PK and PD characteristics of GP2411 and the reference product EU-Prolia were further investigated in the target population of postmenopausal women with osteoporosis in study CGP24112301. The PK parameters AUCinf and Cmax were similar between the GP2411 and the EU-Prolia group after the first dose and thus, the applicant could demonstrate comparable PK between GP2411 and EU-Prolia. Regarding PD, the point estimate of the ratio (GP2411/EU-Prolia) of the geometric mean for AUEC of %CfB in CTX after the first dose was 1.00 with the corresponding 95% CI being [0.98; 1.01]. Thus, the primary PD endpoint was met. These

results were further supported by secondary PD endpoints showing that the mean %CfB in CTX/PINP serum concentration time profiles are comparable between the groups.

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

2.6.5. Clinical efficacy

The overall clinical development program included two pivotal studies to demonstrate PK and PD similarity between GP2411 and the reference product. Efficacy was assessed only in Study CGP24112301. The purpose of this study was to demonstrate similarity in PK, PD, efficacy and safety between GP2411 and EU-Prolia in female subjects with PMO. For an overview of Study CGP24112301, please refer to the table below.

Table 23. Summary of studies contributing to the efficacy assessment of GP2411

Study No.	Study objective Population	Number of subjects treated (SAF)	Treatment duration	Dosage and batch numbers	Efficacy endpoints
Active-controlled studies, randomized and double-blind studies					
CGP24112301 (short: 301) Integrated PK and PD, confirmatory efficacy and safety study	Similarity of GP2411 and EU-Prolia in terms of efficacy, PK, PD, safety, and immunogenicity Female subjects with PMO	N=527 TP1: GP2411: N=263 EU-Prolia: N=264 TP2: GP2411/GP2411: N=253 EU-Prolia/EU-Prolia: N=125 EU-Prolia/GP2411: N=124	3 doses at 26-week intervals Total duration: 78 weeks, including 26 follow up after last dose	GP2411 or EU-Prolia: 60 mg/mL PFS Dosage for both products: 60 mg, 3 s.c. injections (2 in TP1 and 1 in TP2), including a switch from EU-Prolia to GP2411 for the third dose in a subgroup of subjects Batch numbers: GP2411: JZ6970, HZ9550 EU-Prolia: 1112611A, 1096043B, 1108204A	Primary efficacy endpoint: %CfB in LS-BMD at Week 52 Secondary efficacy endpoints: %CfB in LS-BMD, FN-BMD, TH-BMD at Week 26, Week 52, and Week 78 PD endpoints supporting the efficacy assessment (primary PD endpoint: AUEC of %CfB in serum CTX, after first dose)

2.6.5.1. Dose response study(ies)

No dose response studies were performed and are not deemed necessary in the biosimilarity setting.

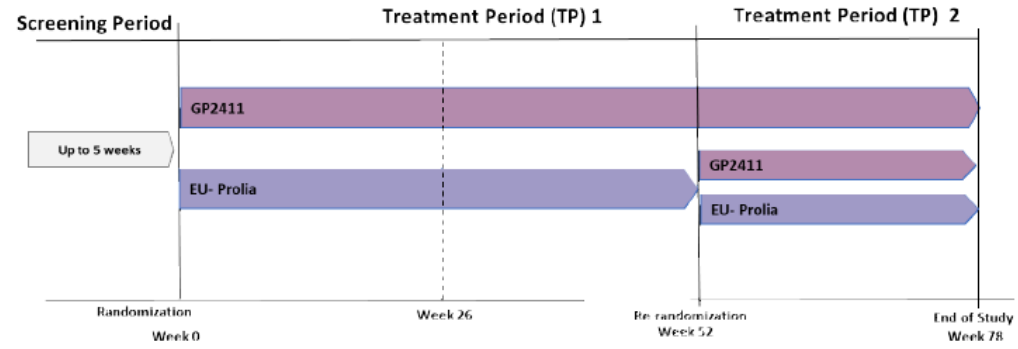
2.6.5.2. Main study(ies)

Study CGP24112301

This was a randomized, double-blind, multicentre integrated phase I/III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity of GP2411 (proposed denosumab biosimilar) and Prolia (EU-authorized). The study had two arms in the first treatment period, and 3 arms in the second treatment period. The total study duration was up to 83 weeks. The study comprised a screening period of up to 5 weeks to assess a subject's eligibility and two treatment periods: TP1 (Day 1 to Week 52) and TP2 (Week 52 to Week 78). Approximately 492 women with PMO were planned to be randomized on Day 1 in a 1:1 ratio to receive either two 60 mg s.c. doses of GP2411 or EU-Prolia during TP1. At Week 52, subjects in the latter group were re-randomized 1:1 to either continue with a third dose of EU-Prolia or switch to GP2411 for TP2.

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

Table 24. Study design



Primary endpoint analyses took place at the end of TP1 (at Week 52)

Methods

- **Study Participants**

Inclusion criteria

1. Signed informed consent had to be obtained prior to participation in the study.

2. Postmenopausal women, diagnosed with osteoporosis.

Postmenopausal status was defined as at least 12 consecutive months of amenorrhea prior to date of screening, for which there was no other obvious pathological or physiological cause. [For CZ only: Postmenopausal status was defined as at least 12 consecutive months of amenorrhea prior to date of screening for which there was no other obvious pathological or physiological cause and by elevated serum FSH level assessed by central laboratory at screening]

3. Aged ≥55 and ≤80 years at screening

4. Body weight ≥50 kg and ≤90 kg at screening

5. Absolute bone mineral density consistent with T-score ≤-2.5 and ≥-4.0 at the lumbar spine as measured by DXA during the Screening Period

6. At least two vertebrae in the L1-L4 region (vertebrae to be assessed by central reading of lateral spine X-ray during the Screening Period) and at least one hip joint are evaluable by DXA

Exclusion Criteria

Subjects meeting any of the following criteria were not eligible for inclusion in this study.

1. Use of other investigational drugs within 5 half-lives of the drug or until the expected pharmacodynamic effect of the drug has returned to baseline, whichever is longer, or longer if required by local regulations

2. Previous exposure to denosumab (Prolia/Pralia, Xgeva/Ranmark, or biosimilar denosumab)

3. History of hypersensitivity to any recombinant protein drugs or any of the excipients used in GP2411 or Prolia

4. History and/or presence of one severe or more than two moderate vertebral fractures (as determined by central reading of lateral spine X-ray during the Screening Period)

5. History and/or presence of hip fracture

6. Presence of active healing fracture according to assessment of investigators

7. History and/or presence of bone metastases (see also exclusion criterion #25), bone disease, metabolic disease (except osteoporosis) that could interfere with the interpretation of the results, e.g. Paget's disease, rheumatoid arthritis, ankylosing spondylitis, osteomalacia, osteogenesis imperfecta, osteopetrosis, Cushing's disease, hyperprolactinemia or malabsorption syndrome

8. Ongoing use of any osteoporosis treatment (other than calcium and vitamin D supplements). Following rules for wash-out periods for osteoporosis treatments had to be adhered to:

- Drugs being investigated for osteoporosis
- Romosozumab: dose received at any time
- Strontium or fluoride (for osteoporosis): dose received at any time
- Intravenous bisphosphonates: dose received within 5 years prior to screening
- Oral bisphosphonates
    - >3 years of cumulative use prior to screening
    - any dose received within 12 months prior to screening
- Teriparatide or any PTH analogs: dose received within 12 months prior to screening
- Tibolone, oral or transdermal estrogen, selective estrogen receptor modulators: dose received within 12 months prior to screening
- Calcitonin: dose received within 6 months prior to screening
- Cinacalcet: dose received within 3 months prior to screening

9. Systemic glucocorticosteroids (≥5 mg prednisone equivalent per day for ≥10 days or a total cumulative dose of ≥50 mg) within the past 3 months before screening

10. Other bone active drugs including heparin, anti-convulsives (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin releasing hormone agonists, anabolic steroids, within the past 3 months before screening

11. Oral or dental conditions:

- osteomyelitis or history and/or presence of ONJ
- presence of risk factors for ONJ (e.g. periodontal disease, poorly fitting dentures, invasive dental procedures such as tooth extractions in 6 months before screening)
- active dental or jaw condition which requires oral surgery
- planned invasive dental procedure

12. Current uncontrolled status of hypothyroidism or hyperthyroidism

13. History and/or current hypoparathyroidism or hyperparathyroidism, irrespective of current controlled or uncontrolled status

14. Vitamin D deficiency, defined as 25 (OH) vitamin D serum level <50 nmol/L (<20 ng/mL). An appropriate vitamin D dose in addition to vitamin D supplementation was permitted at the investigator's discretion and subjects had to be retested during the screening period or rescreened.

15. Current hypocalcemia, defined as calcium <2.10 mmol/L (<8.42 mg/dL) or hypercalcemia, defined as calcium >2.62 mmol/L (>10.50 mg/dL); subjects must have normal albumin values 32-55 g/L (3.2-5.5 g/dL) according to central laboratory normal range.

16. Known intolerance to, or malabsorption of calcium or vitamin D supplements

17. History and / or presence of a severe allergic reaction (e.g. anaphylaxis)

18. History and/or presence of significant cardiac disease as per investigator's discretion, including but not restricted to:

- ECG abnormalities at screening indicating significant risk of safety for subjects participating in the study
- history and/or presence of myocardial infarction within 6 months before screening
- history and/or presence of NYHA class III or IV heart failure

19. Subjects having at screening any of the following hematology values:

- Hemoglobin <10.0 g/dL (<100 g/L)
- White blood cell (WBC) count <3,500/µL (< 3.5 x 109 /L), or neutrophil count <2,000/µL (< 2.0 x 109 /L), or platelet count <125,000/µL (< 125 x 109 /L)

20. Renal impairment manifesting with an estimated glomerular filtration rate <45 mL/min

21. Cirrhosis of the liver, unstable liver disease, or elevated liver function tests to the order of ALT or AST or ALP >2 times upper limit of normal

22. Presence of clinically significant active infections (as per investigator's discretion) that could increase the risk associated with study participation

23. Positive serology indicating Hepatitis B or Hepatitis C infections

24. Positive serology for HIV infection or known diagnosis of AIDS

25. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases

26. Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, made the subject inappropriate for entry into this study

27. Known alcohol, drug or substance abuse within 12 months prior to screening

28. Subjects who were legally institutionalized, or subjects under judicial protection

29. Subjects with an immediate family member (i.e., spouse, parent/legal guardian, sibling or a child) being a member of study site staff or being a member of the sponsor's study team

- **Treatments**

Each subject was planned to receive 3 s.c. doses of study drug (GP2411 or EU-Prolia) at 26-week intervals. GP2411 and EU-Prolia were both supplied as pre-filled syringes containing 1 mL of liquid with 60 mg of denosumab (60 mg/mL).

Additional study treatments

According to the Prolia label, it is important that all subjects receiving denosumab must have an adequate intake of calcium and vitamin D (Prolia SmPC, Prolia US PI). Therefore, from screening (Visit 1) until the end of study, all subjects had to receive at least 1000 mg of elemental calcium and 800 IU vitamin D daily.

- **Objectives**

Primary objectives

- To demonstrate similar efficacy between GP2411 and EU-Prolia, in terms of BMD
- To demonstrate similar PD between GP2411 and EU-Prolia, in terms of the bone resorption marker CTX

Secondary objectives

TP1 (Day 1–– Week 52)

- To compare GP2411 and EU-Prolia in terms of PK, PD, efficacy, safety, and immunogenicity

TP2 (Week 52–- Week 78)

- To further evaluate and compare GP2411 and EU-Prolia in terms of PK, PD, efficacy, safety and immunogenicity, after transitioning 50% of subjects on Prolia to GP2411.

- **Outcomes/endpoints**

Primary endpoints

- Percent change from baseline (%CfB) in lumbar spine BMD (LS-BMD) at Week 52
- AUEC after first dose, of %CfB in serum CTX

Secondary endpoints

Efficacy

- %CfB in BMD at lumbar spine, femoral neck, and total hip (LS-BMD, FN-BMD, TH-BMD) at Week 26
- %CfB in BMD: FN-BMD and TH-BMD at Week 52
- %CfB in LS-BMD, FN-BMD, TH-BMD at Week 78

PD

- CTX and PINP serum concentrations as per visit schedule up to Week 52
- CTX and PINP serum concentrations as per visit schedule from Week 52 up to Week 78

PK

- Serum PK parameters AUCinf and Cmax after first dose
- Denosumab serum concentrations as per visit schedule up to Week 52
- Denosumab serum concentrations as per visit schedule from Week 52 up to Week 78

Safety

- Fractures, vital signs, laboratory safety assessments, injection site reactions, electrocardiogram, occurrence of adverse events and serious aEs up to Week 52
- Fractures, vital signs, laboratory safety assessments, injection site reactions, ECG, occurrence of aEs and serious aEs from Week 52 up to Week 78

Immunogenicity

- Development of binding and neutralizing anti-drug antibodies (ADAs) up to Week 52
- Development of binding and neutralizing ADAs from Week 52 up to Week 78

- **Sample size**

The calculation was based on the following assumptions:

Table 25. Assumptions for sample size calculation

Endpoint	%CfB in LS-BMD	AUEC of %CfB CTX	AUCinf	Cmax
Assumed distribution	LS-BMD ~ Normal	log(AUEC) ~ Normal	log(AUCinf) ~ Normal	log(Cmax) ~ Normal
Assumed variation	SD = 4.08%	CV% = 21.4%	CV% = 33.5%	CV%= 33.1%
Expected difference between treatments	0%	5%	5%	5%
Correlation coefficient between the endpoints		0.6*		0.5**

* Correlation between %CfB of LS-BMD and log(AUEC)

100,000 random samples of sample size of 418 evaluable patients (209 evaluable patients per arm) were generated from a multivariate normal distribution as defined in the table above leading to a sample size of 492 patients (246 per arm) including dropouts. Using the testing requirements that were defined in table below, each co-primary endpoint was tested for each random sample. If all four tests were passed, then the sample was an overall success. The overall power was estimated as the percentage of overall successes out of the 100,000 random samples. Using the above simulation, a power of 90.4% was obtained for simultaneously passing all equivalence tests for the coprimary endpoints.

Table 26. Testing specifications for combined requiredments

Requirement	FDA/EMA %CfB in LSBMD[1]	EMA AUEC of %CfB CTX	PMDA AUCinf	PMDA Cmax
Equivalence margin	(-1.45%, +1.45%)	(80%, 125%)	(80%, 125%)	(80%, 125%)
Expected difference between treatment arms	0%	5%	5%	5%
Power for each endpoint	90.4%	> 99.9%	>99.9%	>99.9%
Two-sided alpha level	5%	5%	10%	10%
Drop-out rate	15% for FAS[2]			

[1] The FDA/EMA for %CfB in LS-BMD requirement is more stringent than the PMDA requirement. The PMDA requirement will therefore be automatically met once the FDA/EMA requirement has been met.
[2] The EMA margin has only been updated from (-2.00%, 2.00%) to (-1.45%, 1.45%) after enrollment had been closed. However, the 15% drop-out rate is still valid for exclusion from PPS based on actual drop-out and protocol deviation exclusion rate.

- **Randomisation and Blinding (masking)**

Randomization on Day 1

At Day 1 (Visit 2), subjects were randomized in a 1:1 ratio to receive either GP2411 or EU-Prolia with approximately 246 subjects in each arm. Randomization on Day 1 was stratified.

Re-randomization at Week 52

At Week 52, all subjects in the GP2411 group continued treatment with a third dose of GP2411. Subjects who had received EU-Prolia during TP1 were re-randomized in a 1:1 ratio to either continue treatment with a third dose of EU-Prolia or switch to GP2411 during TP2. Rerandomization at Week 52 was not stratified.

Stratified randomization

Randomization on Day 1 for the TP1 was stratified by region (US, Rest of World and Japan), age group (<65 years/ ≥65 years), prior bisphosphonates use (yes/ no) and body weight group (<70 kg/ ≥70 kg).

Only a subset of the stratification factors was relevant for each of the co-primary analyses, and only the relevant factors were included in the statistical model for each co-primary endpoint.

• Region was included as an administrative stratification factor in order to ensure a balanced allocation of subjects in each region for relevant region-specific subgroup analyses.

• Age group was added as stratification factor as fracture incidence rate increases significantly after the age of 65 years with primary endpoint LS-BMD not being a sensitive predictor of fracture rates below the age of 65 years.

• Prior treatment with bisphosphonates (yes/ no) was included as a stratification factor to balance prior treatment heterogeneity within the selected population in the study.

• Body weight was considered a major influencing factor on the PK endpoints.

Blinding

Subjects, investigators, and the sponsor remained blinded to study drug throughout the study, except in cases indicated below. The identity of the study drugs could not be concealed as the appearances of the syringes differed. To maintain the double-blind design of the study, unblinded staff at the study site handled the study drug. Unblinded site staff did not perform any clinical assessments. EU-Prolia and GP2411 open label supply was provided to the unblinded site pharmacist. To ensure that the treatment was blinded to the subject and the investigator, receipt, handling and administration of the s.c. injection was performed by

unblinded study site personnel not involved in study assessments. All unblinded study documentation was kept strictly confidential and was not accessible by the blinded site staff. To maintain blinding for the subject, either a screen was used, or the subject was asked to wear a blindfold during the three s.c. injections.

Site staff

Except for any unblinded site staff identified below, all site staff (including study investigator and study nurse) were blinded to study drug throughout the study.

Sponsor staff or delegate

The following unblinded sponsor or delegate (CRO) roles were required for this study:

• Unblinded field monitor(s)

• Unblinded clinical staff managing drug supply at site or interacting with unblinded field monitor(s)

• Unblinded designated study team members for primary endpoint readout (Week 52)

• Unblinded quality assurance and compliance clinical operations staff

After all subjects had completed Week 52 assessment and after the interim database lock for the primary endpoint readout, designated study team members were unblinded to the initial study drug assignment. Subjects, investigators, and the study team who were involved in ongoing study conduct remained blinded until final database lock.

- **Statistical methods**

Analysis sets

The following data sets were used for analysis of the study data:

The Treatment Period 1 Randomised Analysis Set (TP1 RAS) consisted of all patients who were randomized in TP1, including those that were not treated.

The Treatment Period 1 Full Analysis Set (TP1 FAS) was a subset of TP1 RAS and consisted of all patients who were randomized into TP1, who received at least one dose of study medication and for whom at least one post-baseline LS-BMD value (either at Week 26 or at Week 52 or at both visits) was available. Patients were analysed according to the treatment randomised to.

The Treatment Period 1 Safety Set (TP1 SAF) consisted of all patients who received at least one dose of study medication. Patients were analysed according to the treatment received.

The Per-Protocol Set (PPS) was a subset of TP1 RAS and was characterised by the following criteria:

- The LS-BMD assessments at baseline and Week 52 were available.
- The patients received treatment according to protocol at Day 1 and Week 26.
- They experienced no relevant protocol deviations which would affect LS-BMD up to Week 52.

The PD Analysis Set (PDS) was a subset of the TP1 RAS and was characterised by the following criteria:

- CTX values were available in order to be able to calculate the AUEC value for the primary analysis.
- The patients received treatment according to protocol at Day 1.
- They experienced no relevant protocol deviations which would affect CTX measurements up to Week 26.

The PK analysis set (PKS) was a subset of the TP1 RAS and was characterised by the following criteria:

- At least one PK primary endpoint (Cmax or AUCinf) was evaluable.
- The patients received treatment according to protocol at Day 1.
- They experienced no relevant protocol deviations affecting the PK parameters up to Week 26.

The Treatment Period 2 Randomised Analysis Set (TP2 RAS) was a subset of TP1 RAS and consisted of all patients who were re-randomised in TP2, including those that were not treated in TP2.

The Treatment Period 2 Full Analysis Set (TP2 FAS) was a subset of the TP2 RAS and consisted of all patients who were re-randomised into TP2 and for whom at least one TP2 efficacy, PD or PK value was available. Patients were analysed according to the treatment randomised to.

The Treatment Period 2 SAF (TP2 SAF) consisted of all patients who received at least one dose of study medication in TP2. Patients were analysed according to the treatment received in Treatment Period 2.

Primary analysis

%CfB in LS-BMD

The analysis was performed in the PPS and in the TP1 FAS due to different requirements of regulatory bodies.

The following statistical hypotheses were tested to assess equivalence between GP2411 and Prolia in terms of %CfB in LS-BMD at Week 52.

$H0: |GP2411 - Prolia| \geq \Delta$ versus $H1: |GP2411 - Prolia| < \Delta$

Therapeutic equivalence in terms of %CfB in LS-BMD was concluded if the 95% CI of the difference was contained within the interval [-1.45%, 1.45%].

A mixed-model repeated measures (MMRM) analysis was performed for %CfB as the endpoint including the following variables: treatment (GP2411, Prolia), prior bisphosphonate use (yes/ no), DXA machine type (Lunar, Hologic), time (visits Week 26, Week 52), the interaction between time (visits Week 26, Week 52) and treatment (GP2411, Prolia), baseline LS-BMD values as a continuous covariate.

Stratification factor region (US, Rest of World, Japan) was considered an administrative stratification factor and was therefore not included in the statistical model. Stratification factor age (<65 years/ ≥65 years) could best be assumed to have a linear effect on LS-BMD (van Schaik et al 2015) and therefore using the %CfB in LS-BMD as primary endpoint and including LS-BMD Baseline value as covariate should already account for the change in LS-BMD with age. Stratification factor prior bisphosphonate use (yes/ no) was identified as a potential source of heterogeneity for the primary endpoint of LS-BMD that cannot be assured to be completely controlled though the use of inclusion/exclusion criteria and was therefore included in the model. Stratification factor body weight group (<70 kg/ ≥70 kg) was not expected to have a relevant impact on LS-BMD and was therefore not included in the model for LS-BMD. This stratification factor was set up to ensure interpretable PK analyses. Despite a percentage change was used as endpoint and should mitigate the influence of DXA machine types, the model was also adjusted for DXA machine type to sort out any concern.

The most flexible covariance matrix being unstructured was assumed, that is, all variance and covariance parameters are estimated from the data. This allows adjustment for correlation in LS-BMD values across visits within patients.

AUEC of %CfB in serum CTX concentrations

The primary analysis for the AUEC of %CfB in serum CTX concentrations after the first dose were based on the PDS.

The assessment of PD similarity was based upon the 95% cIs of the ratio of the geometric means (GP2411/Prolia) for the AUEC of %CfB in serum CTX concentrations after first dose, which had to be contained entirely within the pre-specified acceptance interval of [0.80, 1.25].

If μPK,T and μPK,R denote the respective population means for test and reference of the PK parameter at Week 26, then the following null and alternative hypotheses were tested for both parameters:

$H0$: $\mu PK,T\ \mu PK,R \leq 0.80\ or : \mu PK,T\ \mu PK,R \geq 1.25$ versus $H1$:$0.80 < \mu PK,T\ \mu PK,R < 1.25$

Analysis of covariance (ANCOVA) was performed on the log-transformed AUEC. The ANCOVA model included the treatment as fixed factor and log(baseline CTX) value as continuous covariate.

Stratification factors, age, prior bisphosphonate use, weight and region, were used in the study for other reasons than accounting for the impact on AUEC of %CfB in CTX and therefore were not included in the model.

Sensitivity analyses for %CfB in LS-BMD

Sensitivity analysis to assess robustness of normality assumption of MMRM

In case the residuals of the MMRM for the %CfB LS-BMD analysis were not approximately distributed as normal (i.e. as assessed using a Q-Q plot) then a 95% nonparametric Hodges-Lehmann CI for the difference between the treatment groups at Week 52 on the subset of patients with a Week 52 %CfB in LS-BMD value available was also calculated.

Sensitivity analysis to assess robustness of MAR assumption for MMRM

The primary MMRM analysis model for %CfB in LS-BMD on the TP1 FAS assumed missing data is MAR. A sensitivity analysis in form of a tipping point analysis was carried out using multiple imputation (MI) methods to impute missing %CfB in LS-BMD at Week 52 values not directly related to the COVID-19 pandemic by making estimated values in a treatment arm worse. Values related to COVID-19 pandemic were considered to be missing at random and therefore were not explicitly imputed. The MI method for missing data in this analysis was based on the algorithm proposed by Carpenter et al 2013 and adapted to the biosimilar setting according to Koch 2008. Values were imputed separately for the biosimilar arm and reference arm. In order to avoid bias in the direction of making arms more similar, the imputation for one arm was made worse by subtracting the margin δ from the mean of LS-BMD of the distribution, which the values for imputation were drawn from. The parameter δ ranged from -2.00% to 0% using 0.05% steps.

Sensitivity to assess impact of forced randomisations

Equivalence analysis based on the TP1 FAS was repeated as sensitivity analysis excluding those patients that were forced randomised (assigned to the next free randomisation number on the randomisation list corresponding to the treatment available at site in case of drug supply issue) in the IRT system.

Secondary analyses

Efficacy endpoints

The endpoints, BMD measurement from DXA scan with location lumbar spine, femoral neck, and femur and associated %CfB, were analysed descriptively.

PD endpoints

CTX and PINP serum concentrations values and associated %CfB were analysed by summary statistics.

PK endpoints

The analysis for the PK parameters after the first dose for AUCinf and Cmax were based on the PKS.

The assessment of PK similarity was based upon the 90% cIs for the ratio of the geometric means (test/reference) for the AUCinf and Cmax which had to be contained entirely within the pre-specified PK acceptance interval of [0.80, 1.25].

If $\mu PK,T$ and $\mu PK,R$ denote the respective population means for test and reference of the PK parameter at Week 26, then the following null and alternative hypotheses were tested for both parameters:

$H0$: $\mu PK,T$ $\mu PK,R \leq 0.80$ or : $\mu PK,T$ $\mu PK,R \geq 1.25$ versus $H1$:$0.80 < \mu PK,T$ $\mu PK,R < 1.25$

ANCOVA was performed on the log-transformed PK parameters. The ANCOVA model included treatment as fixed factor and weight as continuous covariate.

Stratification factors age, prior bisphosphonate use and region were implemented for other reasons than impact on PK parameters (see Section 4.6.2.1) and therefore were not included in the model.

Results

- **Participant flow**

A total number of 1158 subjects were screened for eligibility, of whom 527 subjects were randomized into one of the two treatment groups. Most subjects were enrolled in European countries.

The number of re-screened subjects and the reasons for screen failure are summarized in the table below.

Table 27. Subject disposition (all subjects screened)

Disposition/Reason	Total N=1158 n (%)
Screened	1158 (100)
Re-screened	80 (6.9)
Not Randomized	631 (54.5)
Adverse event	2 (0.2)
Lost to follow-up	1 (0.1)
Physician decision	50 (4.3)
Screen failure	492 (42.5)
Subject decision	86 (7.4)
Randomized	527 (45.5)
Re-randomized at Week 52	502 (43.4)

Subject disposition during TP1

The following table summarizes the subject disposition and the reasons for early study discontinuations up to the end of TP1.

Table 28. Subject disposition – TP1 (TP1 RAS)

Table 10-2 Subject disposition – TP1 (TP1 RAS)

Disposition/Reason	GP2411 N=263 n (%)	EU-Prolia N=264 n (%)
Randomized subjects	263 (100)	264 (100)
Treated	263 (100)	264 (100)
Completed TP1	253 (96.2)	249 (94.3)
Discontinued from study in TP1	10 (3.8)	15 (5.7)
Reason for discontinuation		
Adverse event	1 (0.4)	3 (1.1)
Death	1 (0.4)	0
Lost to follow-up	0	1 (0.4)
Physician decision	0	2 (0.8)
Subject decision	8 (3.0)	9 (3.4)

Subject disposition during TP2

The following table summarizes the subject disposition and the reasons for early study discontinuations up to the end of TP2.

Table 29. Subject disposition – TP2 (TP2 RAS)

Disposition/Reason	GP2411/GP2411 N=253 n (%)	EU-Prolia/EU-Prolia N=125 n (%)	EU-Prolia/GP2411 N=124 n (%)
Re-randomized subjects	253 (100)	125 (100)	124 (100)
Treated in TP2	253 (100)	125 (100)	124 (100)
Completed TP2	253 (100)	123 (98.4)	124 (100)
Discontinued from study in TP2	0	2 (1.6)	0
Reason for discontinuation			
Lost to follow-up	0	1 (0.8)	0
Subject decision	0	1 (0.8)	0

Protocol deviations by category in TP1

All protocol deviations are summarized by category in the following table for the TP1 analysis. Most protocol deviations were categorized as "Other". The most frequent "other" protocol deviations were "DXA scan performed outside of allowed time limit", "ADA sampling not performed", "PD sampling not performed", "PK sampling not performed", and "Planned visit not performed on site but via phone instead due to COVID-19".

Table 30. Protocol deviations by category, TP1 (TP1 RAS)

	GP2411 N=263 n (%)	EU-Prolia N=264 n (%)
Subjects with at least one protocol deviation	120 (45.6)	136 (51.5)
Protocol deviation		
Selection Criteria Not Met	6 (2.3)	2 (0.8)
Treatment Deviation	31 (11.8)	26 (9.8)
Prohibited Concomitant Medication	15 (5.7)	18 (6.8)
Other deviations	103 (39.2)	113 (42.8)

A subject with multiple occurrences of a protocol deviation category is counted only once in the protocol deviation category. Subjects may have protocol deviations in more than one protocol deviation category.

Protocol deviations by category in TP2

Protocol deviations are summarized by category in the following table for the TP2 analysis. Most protocol deviations were categorized as "Other". The most frequent "other" protocol deviations were X-ray performed outside of allowed time limit and DXA scan performed outside of allowed time limit.

Table 31. Protocol deviations by category, TP2 (TP2 RAS)

	GP2411/GP2411 N=253 n (%)	EU-Prolia/EU-Prolia N=125 n (%)	EU-Prolia/GP2411 N=124 n (%)
Subjects with at least one protocol deviation	103 (40.7)	51 (40.8)	52 (41.9)
Protocol deviation			
Treatment Deviation	11 (4.3)	12 (9.6)	8 (6.5)
Prohibited Concomitant Medication	5 (2.0)	2 (1.6)	3 (2.4)
Other Deviation	100 (39.5)	45 (36.0)	51 (41.1)

Protocol deviations and analysis restrictions leading to exclusion from analysis sets

Exclusion from PPS

A total of 30 subjects (11.4%) in the GP2411 group and 34 subjects (12.9%) in the EU-Prolia group were excluded from the PPS due to early discontinuations and protocol deviations, as shown in the following table. For some subjects, multiple protocol deviations or other reasons led to exclusion from the PPS.

Table 32. Reasons for exclusion from PPS (TP1 RAS)

	GP2411 N=263 n (%)	EU-Prolia N=264 n (%)
Total exclusions	30 (11.4)	34 (12.9)
Subjects discontinued study before Week 52	10 (3.8)	15 (5.7)
Protocol deviations leading to exclusion from PPS	20 (7.6)	21 (8.0)
Selection criteria not met	4 (1.5)	1 (0.4)
Exclusion criterion 10 met: Other bone active drugs within the past 3 months before screening	3 (1.1)	0
Inclusion criterion 5 not met: absolute BMD consistent with T-score ≤-2.5 and ≥-4.0 at the lumbar spine as measured by DXA scan during the screening period	1 (0.4)	0
Exclusion criterion 2 met: Previous exposure to denosumab	0	1 (0.4)
Prohibited concomitant medication	15 (5.7)	17 (6.4)
Other reasons: Lumbar spine BMD (DXA scan) performed more than 14 days after dosing	4 (1.5)	3 (1.1)

Exclusion from PDS

A total of 35 subjects (13.3%) in the GP2411 group and 51 subjects (19.3%) in the EU-Prolia group had to be excluded from the PDS, partly due to protocol deviations but also due to other reasons, as shown in the following table (for some subjects, multiple criteria lead to exclusion).

Table 33. Exclusions from PDS (TP1 RAS)

Table 10-5 Exclusion from PDS (TP1 RAS)

	GP2411 N=263 n (%)	EU-Prolia N=264 n (%)
Total exclusions	35 (13.3)	51 (19.3)
Protocol deviations leading to exclusion from PDS	15 (5.7)	14 (5.3)
Selection Criteria not met	3 (1.1)	1 (0.4)
Exclusion criterion 10 met: Other bone active drugs within the past 3 months before screening	3 (1.1)	0
Exclusion criterion 2 met: Previous exposure to denosumab	0	1 (0.4)
Prohibited Concomitant Medication	13 (4.9)	13 (4.9)
Other reasons for exclusion from PDS (AUEC value missing or excluded from analysis)	22 (8.4)	38 (14.4)
Required visit samples are missing or excluded*	14 (5.3)	27 (10.2)
Pre-dose sample at visit 2 not taken prior treatment	4 (1.5)	1 (0.4)
Pre-dose visit 2 CTX concentration < 24% above LLOQ	3 (1.1)	10 (3.8)
Visit 4 to visit 6 denosumab serum concentrations below LLOQ	1 (0.4)	0
Pre-dose visit denosumab serum concentrations above LLOQ	0	5 (1.9)

Source: Table 14.1-2.3 and Table 14.1-6.1

For some subjects, multiple protocol deviations or other reasons lead to exclusion from the PDS.

* As per definition, this category also includes those samples that were excluded due to sampling time window violations or sample collection in a non-fasting state at Visit 2 and Visit 11.

Exclusion from PKS

Three subjects (1.1%) in the GP2411 group and 6 subjects (2.3%) in the EU-Prolia group had to be excluded from the PKS, as shown in the following table.

Table 34. Exclusion from PKS (TP1 RAS)

	GP2411 N=263 n (%)	EU-Prolia N=264 n (%)
Total exclusions	3 (1.1)	6 (2.3)
Protocol deviations leading to exclusion from PKS	0	1 (0.4)
Selection Criteria not met (Exclusion criterion 2 met: Previous exposure to denosumab)	0	1 (0.4)
Other reasons for exclusion from PKS (Cmax and AUCinf both are missing or excluded from analysis)	3 (1.1)	5 (1.9)
No usable Visit 4 nor Visit 5 nor Visit 6 concentration available	3 (1.1)	2 (0.8)
Pre-dose > LLoQ and > 5% Cmax.	0	3 (1.1)

- **Recruitment**

Study initiation date: 14-Jun-2019 (date of first ICF signing)

Study completion date: 22-Apr-2022 (last subject last visit)

Interim database lock: 18-Feb-2022

Database lock date: 4-Jul-2022 (date of final DBL)

There were two database locks, one for the planned interim analysis at the end of TP1 at Week 52 and one for the final analyses at study end (end of TP2 at Week 78). Both the planned interim analysis and the final analysis were conducted according to the protocol and the statistical analysis plan. The involved staff for the interim analysis signed for their adherence to a blinded/unblinded team charter.

- **Conduct of the study**

Protocol identification: CGP24112301; EudraCT no. 2018-003523-11; date of final protocol (v00, original protocol): 28-Sep-2018

The study protocol was amended six times.

Amendment 1 (released on 10-Dec-2018): The main purpose of this first amendment was to address FDA IND review comments on the use of appropriate terminology, e.g. when referring to US-licensed Prolia and EU-authorized Prolia.

Amendment 2 (released on 15-Mar-2019) addressed feedback from EMA follow-up scientific advice (13-Dec-2018) and FDA advice on investigational drug application (06-Feb-2019). The following main changes were implemented:

• The sample size calculations were updated to change the CI for the LS-BMD for the FDA requirements to use a 95% CI (previously a 90% CI) in the similarity assessment of the primary endpoint. This resulted in a change in the total sample size from 436 to 522 throughout the protocol.

• The inclusion and exclusion criteria were updated, additional PK, PD and ADA sampling time points were added, the definition of the analysis sets was updated, handling of missing efficacy values was clarified, and a sensitivity analysis was planned. In addition, severity grading of ISRs and other aEs was updated.

• Severity grading of ISRs was updated to align with the CTCAE classification.

Local Amendment 3 (released on 28-Jun-2019) was implemented for Czech Republic only.

This amendment added a FSH test at Screening to confirm menopause and also a urine sediment test at regular intervals.

Local amendment 4 (released on 10-Sept-2019) addressed PMDA findings that were issued in a deficiency letter, and implemented the following changes in Japan only:

• Natural vitamin D was specified as an additional study drug

• Romosozumab was listed as a standalone approved drug excluded for prior or ongoing osteoporosis treatment

• An additional laboratory test at Day -4 was added for testing of calcium levels in Japanese subjects switching from activated vitamin D to natural vitamin D at Visit 1

• The Japanese brand name was added to the respective sections

Amendment 5 was released on 21-Feb-2020, by when the study had recruited more than 200 subjects globally. It addressed FDA's and PMDA's request for a change in data analysis following a second review of the protocol:

• Analysis set for the primary analysis of %CfB in LS-BMD for FDA was updated from PPS to TP1 FAS, which resulted in a reduction of the sample size from 522 to 492 subjects. The PPS was planned as supplementary analysis.

• In addition, SD estimate of %CfB in LS-BMD at Week 52 was updated from 3.96 to 4.08 deriving the SD as pooled SD over the 3 historical published studies instead of using weights based on variance of difference in mean between denosumab and placebo

• The rationale for different stratification factors was clarified.

• This amendment also changed the calcium assessment by shifting from the parameter "albumin adjusted serum calcium" to the parameter "total serum calcium".

• Screening period was prolonged from 28 to 35 days.

• Further minor changes comprised clarifications of a range of laboratory assessments, examinations, and analytical methods; and removal of non-mandatory listings from the planned analyses, some sensitivity analyses for PK and PD endpoints and if study-specific CTX margins.

• To rule out misunderstandings of the statistical testing requirements, the overall hierarchical testing strategy for the different health authorities was presented in tabular format.

Local amendments 3 and 4 were also incorporated into the updated new version of the protocol.

Amendment 6 was released on 30-Oct-2020, by when the study recruitment had already been finished, to address FDA request on missing data, COVID-19 testing and statistic testing strategy from one overall testing to three separate testing strategy:

• To assess a possible impact from SARS-CoV-2 on study outcomes, optional serological testing for SARS-CoV-2 antibodies was introduced to enable sensitivity analyses of clinical parameters, if needed.

• The statistical testing strategy was updated from one overall study testing strategy to three separate testing strategies which address different health authority requirements

• In response to FDA's request for additional information, details were added on the MMRM model, and the handling and statistical analysis of missing data.

- **Baseline data**

Demography during TP1

The key demographics and baseline characteristics for the TP1 are summarized in the following table for the SAF.

Table 35. Demographics and baseline characteristics (TP1 SAF)

Demographic variable	GP2411 (N=263)	EU-Prolia (N=264)
Age (years)		
Mean (SD)	64.6 (6.08)	64.7 (5.78)
Median	64.0	64.0
Min-Max	55-80	55-80
Age category -n (%)		
<65 years	137 (52.1)	139 (52.7)
>=65 years	126 (47.9)	125 (47.3)
Ethnicity -n (%)		
Hispanic or Latino	9 (3.4)	8 (3.0)
Not Hispanic or Latino	253 (96.2)	255 (96.6)
Not reported	1 (0.4)	1 (0.4)
Race -n (%)		
Asian	23 (8.7)	24 (9.1)
-- Japanese	23 (8.7)	23 (8.7)
-- Missing	0	1 (0.4)
Multiple	1 (0.4)	0
White	239 (90.9)	240 (90.9)
Weight (kg)		
Mean (SD)	62.31 (8.993)	63.36 (9.233)
Median	60.80	62.00
Min-Max	50.0-89.0	50.0-90.0
Weight category -n (%)		
<70 kg	209 (79.5)	209 (79.2)
>=70 kg	54 (20.5)	55 (20.8)
Region -n (%)		
Japan	23 (8.7)	23 (8.7)
Rest of World	231 (87.8)	230 (87.1)
US	9 (3.4)	11 (4.2)

Demography during TP2

The key demographics and baseline characteristics for the TP2 are summarized in the following table for the SAF.

Table 36. Demographics and baseline characteristics (TP2 SAF)

Demographic variable	GP2411/GP2411 N=253	Prolia/Prolia N=125	Prolia/GP2411 N=124	Total N=502
Age (years)				
n	253	125	124	502
Mean (SD)	64.6 (6.15)	65.1 (5.97)	64.3 (5.61)	64.6 (5.97)
Median	64.0	65.0	63.0	64.0
Min-Max	55-80	55-77	55-80	55-80
Age category -n (%)				
<65 years	132 (52.2)	61 (48.8)	72 (58.1)	265 (52.8)
>=65 years	121 (47.8)	64 (51.2)	52 (41.9)	237 (47.2)
Ethnicity -n (%)				
Hispanic or Latino	8 (3.2)	2 (1.6)	5 (4.0)	15 (3.0)
Not Hispanic or Latino	244 (96.4)	123 (98.4)	119 (96.0)	486 (96.8)
Not reported	1 (0.4)	0	0	1 (0.2)
Race -n (%)				
Asian	21 (8.3)	14 (11.2)	8 (6.5)	43 (8.6)
-- Japanese	21 (8.3)	13 (10.4)	8 (6.5)	42 (8.4)
-- Missing	0	1 (0.8)	0	1 (0.2)
Multiple	1 (0.4)	0	0	1 (0.2)
White	231 (91.3)	111 (88.8)	116 (93.5)	458 (91.2)
Weight (kg)				
n	253	125	124	502
Mean (SD)	62.42 (9.043)	62.70 (8.957)	63.65 (9.413)	62.79 (9.110)
Median	60.90	62.00	62.95	61.40
Min-Max	50.0-89.0	50.0-90.0	50.0-89.5	50.0-90.0
Weight category -n (%)				
<70 kg	200 (79.1)	104 (83.2)	95 (76.6)	399 (79.5)
>=70 kg	53 (20.9)	21 (16.8)	29 (23.4)	103 (20.5)
Region -n (%)				
Japan	21 (8.3)	13 (10.4)	8 (6.5)	42 (8.4)
Rest of World	223 (88.1)	108 (86.4)	111 (89.5)	442 (88.0)
US	9 (3.6)	4 (3.2)	5 (4.0)	18 (3.6)

Baseline disease characteristics TP1

The baseline characteristics for the TP1 are summarized in the following table for the SAF.

Table 37. Baseline characteristics (TP1 SAF)

Characteristic	GP2411 N=263	EU-Prolia N=264
LS-BMD (g/cm²)		
Mean (SD)	0.7505 (0.06929)	0.7512 (0.06852)
Median	0.7460	0.7455
Min-Max	0.603-0.925	0.605-0.920
LS T-score		
Mean (SD)	-3.1122 (0.41865)	-3.0856 (0.39351)
Median	-3.0000	-3.0000
Min-Max	-4.500--2.500	-4.000--2.500
CTX (ng/mL)		
n	263	263
Mean (SD)	0.4282 (0.25167)	0.4388 (0.32179)
Median	0.4000	0.3890
Min-Max	0.033-1.406	0.033-3.351
PINP (ng/mL)		
n	263	263
Mean (SD)	60.0070 (27.76279)	61.4382 (33.31855)
Median	57.6230	56.9090
Min-Max	10.319-219.574	11.113-256.877
Prior bisphosphonate use -n (%)		
N	214 (81.4)	213 (80.7)
Y	49 (18.6)	51 (19.3)

Baseline disease characteristics TP2

The baseline characteristics for the TP2 are summarized in the following table for the SAF.

Table 38. Baseline characteristics (TP2 SAF)

Characteristic	GP2411/GP2411 N=253	Prolia/Prolia N=125	Prolia/GP2411 N=124	Total N=502
LS-BMD (g/cm²)				
n	253	125	124	502
Mean (SD)	0.7486 (0.06940)	0.7498 (0.06506)	0.7471 (0.07109)	0.7485 (0.06864)
Median	0.7450	0.7400	0.7435	0.7445
Min-Max	0.603-0.925	0.606-0.885	0.605-0.920	0.603-0.925
FN-BMD (g/cm²)				
n	253	125	124	502
Mean (SD)	0.6645 (0.10704)	0.6768 (0.10980)	0.6723 (0.10664)	0.6695 (0.10755)
Median	0.6580	0.6660	0.6665	0.6635
Min-Max	0.438-1.003	0.451-1.026	0.478-0.897	0.438-1.026
TH-BMD (g/cm²)				
n	253	125	124	502
Mean (SD)	0.7399 (0.08836)	0.7562 (0.08455)	0.7455 (0.08871)	0.7453 (0.08760)
Median	0.7370	0.7600	0.7525	0.7485
Min-Max	0.533-1.034	0.529-1.064	0.552-0.945	0.529-1.064
CTX (ng/mL)				
n	253	125	124	502
Mean (SD)	0.4333 (0.25214)	0.4631 (0.38004)	0.4129 (0.25756)	0.4357 (0.29039)
Median	0.4050	0.3960	0.3650	0.3910
Min-Max	0.033-1.406	0.033-3.351	0.033-1.284	0.033-3.351
PINP (ng/mL)				
n	253	125	124	502
Mean (SD)	60.0821 (27.79804)	63.1711 (36.96769)	59.0909 (29.17504)	60.6065 (30.63076)
Median	57.6420	56.0790	55.7700	57.2080
Min-Max	10.319-219.574	11.113-256.877	12.893-167.288	10.319-256.877
Prior bisphosphonate use -n (%)				
N	207 (81.8)	108 (86.4)	93 (75.0)	408 (81.3)
Y	46 (18.2)	17 (13.6)	31 (25.0)	94 (18.7)

- **Numbers analysed**

The analysis sets for the analyses conducted during TP1 based on the interim analysis data corresponding to the primary analysis are summarized in the following table.

Table 39. Analysis sets, TP1 (TP1 RAS)

Analysis set	GP2411 N=263 n (%)	Prolia N=264 n (%)	Total N=527 n (%)
TP1 RAS	263 (100.0)	264 (100.0)	527 (100.0)
TP1 SAF	263 (100.0)	264 (100.0)	527 (100.0)
TP1 FAS	255 (97.0)	257 (97.3)	512 (97.2)
PPS	233 (88.6)	230 (87.1)	463 (87.9)
PKS	260 (98.9)	258 (97.7)	518 (98.3)
PDS	228 (86.7)	213 (80.7)	441 (83.7)

The analysis sets for the analyses conducted during TP2 based on final analysis data are summarized in the following table.

Table 40. Analysis sets, TP2 (TP2 RAS)

Analysis set	GP2411/GP2411 N=253 n (%)	Prolia/Prolia N=125 n (%)	Prolia/GP2411 N=124 n (%)	Total N=502 n (%)
TP2 RAS	253 (100.0)	125 (100.0)	124 (100.0)	502 (100.0)
TP2 SAF	253 (100.0)	125 (100.0)	124 (100.0)	502 (100.0)
TP2 FAS	253 (100.0)	124 (99.2)	124 (100.0)	501 (99.8)

- **Outcomes and estimation**

Primary efficacy analysis

%CfB in LS-BMD at week 52 for PPS

The following table summarizes the result of the primary efficacy endpoint %CfB in LS-BMD at Week 52 (TP1) for the PPS.

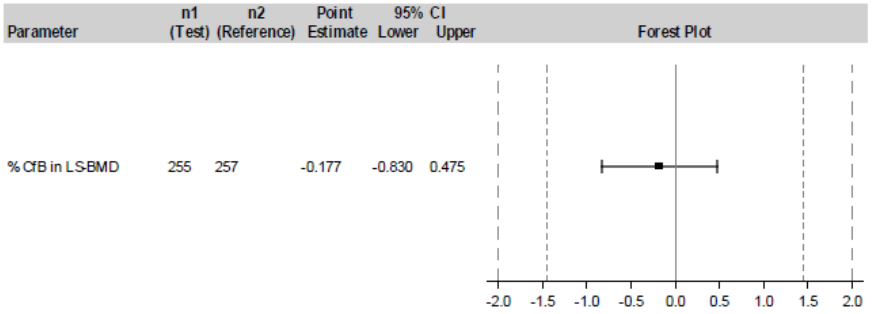
Table 41. Repeated measures analysis of %CfB in LS-BMD at Week 52

	Adjusted mean change (SE)		Comparison of adjusted means: GP2411 vs EU-Prolia		
Comparison	GP2411 (N=233)	EU-Prolia (N=230)	Diff (GP2411 - EU-Prolia)	SE	95% CI
GP2411 vs EU-Prolia	4.955 (0.2634)	5.099 (0.2618)	-0.145	0.3325	(-0.798,0.509)

An MMRM analysis was performed for %CfB in LS-BMD including the following variables: treatment (GP2411, EU-Prolia), prior bisphosphonate use (yes, no), DXA machine type (Lunar, Hologic), visit (Week 26, Week 52), interaction between visit and treatment, and baseline LS-BMD value as a continuous covariate.

The results of the FDA and PMDA-specific analysis of the primary efficacy endpoint %CfB in LS-BMD at Week 52 (TP1) for the TP1 FAS is shown in the following figure.

Figure 9. Adjusted mean difference and 95%CI of the primary endpoint %CfB in LS-BMD at Week 52 (TP1 FAS)



Vertical dashed lines represent equivalence margins: +/-1.45% per FDA requirement and +/-2.00% per PMDA requirement. Missing data is assumed to be MAR.

Point estimate represents difference in GP2411 (Test) to EU-Prolia (Reference).

Secondary efficacy endpoints

%CfB in BMD at lumbar spine at week 26

The summary statistics for LS-BMD during TP1 are shown in the table below for the PPS set.

Table 42. LS-BMD (g/cm²): Summary statistics by treatment group and visit, TP1 PPS

Timepoint	Statistics	GP2411 N=233	Prolia N=230
Baseline	n	233	230
	Mean (SD)	0.7501 (0.06832)	0.7503 (0.06773)
	Median	0.7450	0.7455
	Q1-Q3	0.7050-0.8010	0.7060-0.8100
	Min-Max	0.603-0.920	0.605-0.920
Week 26	n	233	229
	Mean (SD)	0.7770 (0.07126)	0.7777 (0.07049)
	Median	0.7700	0.7650
	Q1-Q3	0.7290-0.8290	0.7300-0.8340
	Min-Max	0.614-0.982	0.612-0.930
% change from baseline	n	233	229
	Mean (SD)	3.6501 (3.76952)	3.6700 (3.68816)
	Median	3.9816	3.8822
	Q1-Q3	1.4360-5.6047	1.2694-5.6671
	Min-Max	-14.006-15.286	-8.214-16.830
Week 52	n	233	230
	Mean (SD)	0.7902 (0.07180)	0.7916 (0.07052)
	Median	0.7860	0.7845
	Q1-Q3	0.7390-0.8450	0.7450-0.8480
	Min-Max	0.627-0.959	0.588-0.943
% change from baseline	n	233	230
	Mean (SD)	5.4199 (3.73480)	5.5867 (3.94663)
	Median	5.4449	5.4424
	Q1-Q3	3.1250-7.6216	3.3375-8.2037
	Min-Max	-6.374-17.406	-8.299-16.176

%CfB in BMD at lumbar spine at week 78

The summary statistics for LS-BMD during TP1 and TP2 are shown in the table below for the TP2 FAS set.

Table 43. LS-BMD (g/cm²): Summary statistics by treatment group and visit, TP1+TP2 (TP2 FAS)

Timepoint	Statistics	GP2411/GP2411 N=253	Prolia/Prolia N=124	Prolia/GP2411 N=124
Baseline	n	253	124	124
	Mean (SD)	0.7486 (0.06940)	0.7502 (0.06519)	0.7471 (0.07109)
	Median	0.7450	0.7425	0.7435
	Q1-Q3	0.7020-0.8010	0.7085-0.7950	0.6930-0.8095
	Min-Max	0.603-0.925	0.606-0.885	0.605-0.920
Week 26	n	253	124	123
	Mean (SD)	0.7748 (0.07222)	0.7773 (0.06961)	0.7751 (0.07294)
	Median	0.7700	0.7590	0.7670
	Q1-Q3	0.7250-0.8260	0.7330-0.8290	0.7260-0.8350
	Min-Max	0.614-0.929	0.630-0.980	0.612-0.930
% change from baseline	n	253	124	123
	Mean (SD)	3.5570 (3.75280)	3.6660 (3.94056)	3.7484 (3.93921)
	Median	3.7879	3.7022	3.8822
	Q1-Q3	1.3072-5.5409	1.1088-5.8827	1.2500-5.6671
	Min-Max	-14.006-15.286	-8.214-19.378	-8.063-12.898
Week 52	n	253	124	124
	Mean (SD)	0.7886 (0.07227)	0.7926 (0.06881)	0.7862 (0.07413)
	Median	0.7820	0.7845	0.7710
	Q1-Q3	0.7340-0.8420	0.7460-0.8335	0.7355-0.8550
	Min-Max	0.627-0.958	0.601-0.997	0.588-0.930
% change from baseline	n	253	124	124
	Mean (SD)	5.4249 (3.80015)	5.7476 (4.51720)	5.3090 (3.90281)
	Median	5.4449	5.0788	5.6187
	Q1-Q3	3.0641-7.7748	3.2537-8.9642	2.7871-7.8816
	Min-Max	-6.374-17.406	-8.299-23.621	-6.383-13.012
Week 78	n	249	123	122
	Mean (SD)	0.8010 (0.07327)	0.8026 (0.06960)	0.7952 (0.07746)
	Median	0.7940	0.7960	0.7955
	Q1-Q3	0.7470-0.8540	0.7530-0.8590	0.7430-0.8600
	Min-Max	0.641-0.970	0.649-0.997	0.626-0.939
% change from baseline	n	249	123	122
	Mean (SD)	6.8222 (3.95225)	7.0694 (4.72955)	6.4212 (4.47102)
	Median	6.7669	6.4865	6.3406
	Q1-Q3	4.7473-9.2545	4.5402-9.7724	3.7940-9.5170
	Min-Max	-6.147-17.647	-9.932-25.460	-5.109-19.883

%CfB in BMD at femoral neck at week 26 and week 52

The summary statistics for FN-BMD during TP1 are shown in the table below for the PPS set.

Table 44. FN-BMD (g/cm²): Summary statistics by treatment group and visit, TP1 PPS

Timepoint	Statistics	GP2411 N=233	Prolia N=230
Baseline	n	233	230
	Mean (SD)	0.6641 (0.10688)	0.6743 (0.10904)
	Median	0.6580	0.6670
	Q1-Q3	0.5760-0.7420	0.5850-0.7650
	Min-Max	0.438-1.002	0.451-1.026
Week 26	n	232	229
	Mean (SD)	0.6775 (0.10859)	0.6868 (0.10931)
	Median	0.6740	0.6800
	Q1-Q3	0.5955-0.7580	0.5930-0.7770
	Min-Max	0.435-1.045	0.475-0.995
% change from baseline	n	232	229
	Mean (SD)	2.0818 (3.38039)	1.8087 (3.18505)
	Median	2.1996	1.8182
	Q1-Q3	0.1625-4.3071	-0.1623-3.8400
	Min-Max	-7.974-16.540	-7.826-18.137
Week 52	n	233	229
	Mean (SD)	0.6797 (0.10995)	0.6921 (0.11224)
	Median	0.6770	0.6820
	Q1-Q3	0.5900-0.7590	0.6060-0.7850
	Min-Max	0.429-1.033	0.489-1.019
% change from baseline	n	233	229
	Mean (SD)	2.4200 (3.70552)	2.6157 (3.26119)
	Median	2.4169	2.7027
	Q1-Q3	0.3115-4.6133	0.4777-4.5643
	Min-Max	-7.860-13.498	-8.696-15.686

%CfB in BMD at femoral neck at week 78

The summary statistics for FN-BMD during TP1 and TP2 are shown in the table below for the TP2 FAS set.

Table 45. FN-BMD (g/cm²): Summary statistics by treatment group and visit, TP1+TP2 (TP2 FAS)

Timepoint	Statistics	GP2411/GP2411 N=253	Prolia/Prolia N=124	Prolia/GP2411 N=124
Baseline	n	253	124	124
	Mean (SD)	0.6645 (0.10704)	0.6765 (0.11019)	0.6723 (0.10664)
	Median	0.6580	0.6650	0.6665
	Q1-Q3	0.5770-0.7430	0.5895-0.7645	0.5775-0.7650
	Min-Max	0.438-1.003	0.451-1.026	0.478-0.897
Week 26	n	252	124	123
	Mean (SD)	0.6775 (0.10907)	0.6875 (0.11199)	0.6860 (0.10543)
	Median	0.6725	0.6745	0.6790
	Q1-Q3	0.5960-0.7590	0.5855-0.7770	0.5990-0.7800
	Min-Max	0.435-1.045	0.475-0.995	0.475-0.908
% change from baseline	n	252	124	123
	Mean (SD)	2.0303 (3.45310)	1.6633 (3.16174)	1.9429 (3.11983)
	Median	2.1580	1.5936	1.8841
	Q1-Q3	0.1882-4.2752	-0.3536-3.5613	0.0000-4.0441
	Min-Max	-9.077-16.540	-6.605-18.137	-7.826-10.420
Week 52	n	253	123	124
	Mean (SD)	0.6798 (0.11006)	0.6952 (0.11189)	0.6879 (0.11096)
	Median	0.6770	0.6800	0.6785
	Q1-Q3	0.5910-0.7610	0.6100-0.7830	0.5980-0.7870
	Min-Max	0.429-1.033	0.489-1.019	0.490-0.937
% change from baseline	n	253	123	124
	Mean (SD)	2.3707 (3.69143)	2.7453 (3.28858)	2.3280 (3.22294)
	Median	2.3401	2.7027	2.5591
	Q1-Q3	0.2454-4.6133	0.4959-4.7009	0.0749-4.4736
	Min-Max	-7.860-13.498	-6.424-15.686	-8.696-9.748
Week 78	n	247	122	122
	Mean (SD)	0.6873 (0.11083)	0.6978 (0.11181)	0.6917 (0.11025)
	Median	0.6850	0.6895	0.6805
	Q1-Q3	0.5990-0.7760	0.6090-0.7840	0.6030-0.7810
	Min-Max	0.453-1.043	0.489-1.019	0.496-0.913
% change from baseline	n	247	122	122
	Mean (SD)	3.2220 (4.03733)	2.9406 (3.92115)	2.6857 (3.64193)
	Median	3.3473	3.2623	2.9526
	Q1-Q3	0.6993-5.6106	0.5229-4.8701	0.6319-5.1471
	Min-Max	-10.000-15.061	-10.661-20.915	-8.473-12.298

%CfB in BMD at total hip at week 26 and week 52

The summary statistics for TH-BMD during TP1 are shown in the table below for the PPS set.

Table 46. TH-BMD (g/cm²): Summary statistics by treatment group and visit, TP1 PPS

Timepoint	Statistics	GP2411 N=233	Prolia N=230
Baseline	n	233	230
	Mean (SD)	0.7401 (0.08843)	0.7499 (0.08769)
	Median	0.7370	0.7560
	Q1-Q3	0.6780-0.7920	0.6870-0.8130
	Min-Max	0.544-1.034	0.529-1.064
Week 26	n	232	229
	Mean (SD)	0.7594 (0.08975)	0.7663 (0.08693)
	Median	0.7600	0.7740
	Q1-Q3	0.6860-0.8130	0.7080-0.8210
	Min-Max	0.568-1.072	0.537-1.079
% change from baseline	n	232	229
	Mean (SD)	2.6475 (2.43928)	2.1178 (2.44627)
	Median	2.5635	2.1477
	Q1-Q3	0.8641-4.2792	0.6192-3.5278
	Min-Max	-3.666-9.486	-5.350-11.065
Week 52	n	233	229
	Mean (SD)	0.7652 (0.09143)	0.7755 (0.08958)
	Median	0.7660	0.7810
	Q1-Q3	0.6980-0.8200	0.7130-0.8350
	Min-Max	0.566-1.076	0.548-1.098
% change from baseline	n	233	229
	Mean (SD)	3.4289 (2.71152)	3.3211 (2.59266)
	Median	3.3094	3.2168
	Q1-Q3	1.5896-5.1560	1.6905-4.9149
	Min-Max	-7.154-14.907	-4.108-11.796

%CfB in BMD at total hip at week 78

The summary statistics for TH-BMD during TP1 and TP2 are shown in the table below for the FAS set.

Table 47. TH-BMD (g/cm²): Summary statistics by treatment group and visit, TP1+TP2 (TP2 FAS)

Table 14.2-4.2 (Page 1 of 2)
TH-BMD (g/cm²): Summary statistics by treatment group and visit, TP1+TP2
TP2 FAS

Timepoint	Statistics	GP2411/GP2411 N=253	Prolia/Prolia N=124	Prolia/GP2411 N=124
Baseline	n	253	124	124
	Mean (SD)	0.7399 (0.08836)	0.7558 (0.08474)	0.7455 (0.08871)
	Median	0.7370	0.7585	0.7525
	Q1-Q3	0.6780-0.7930	0.6990-0.8140	0.6820-0.8070
	Min-Max	0.533-1.034	0.529-1.064	0.552-0.945
Week 26	n	252	124	123
	Mean (SD)	0.7584 (0.08977)	0.7713 (0.08513)	0.7616 (0.08675)
	Median	0.7580	0.7820	0.7680
	Q1-Q3	0.6905-0.8130	0.7175-0.8195	0.6960-0.8210
	Min-Max	0.544-1.072	0.537-1.079	0.553-0.953
% change from baseline	n	252	124	123
	Mean (SD)	2.5435 (2.48329)	2.0993 (2.37544)	2.0139 (2.55450)
	Median	2.4676	2.0037	2.1505
	Q1-Q3	0.8107-4.2113	0.6163-3.5937	0.5882-3.3499
	Min-Max	-3.666-9.486	-4.695-11.065	-6.904-8.915
Week 52	n	253	123	124
	Mean (SD)	0.7641 (0.09173)	0.7811 (0.08498)	0.7695 (0.09133)
	Median	0.7650	0.7830	0.7795
	Q1-Q3	0.6980-0.8200	0.7260-0.8320	0.7010-0.8340
	Min-Max	0.541-1.076	0.555-1.098	0.548-0.969
% change from baseline	n	253	123	124
	Mean (SD)	3.2992 (2.70684)	3.1704 (2.41606)	3.2619 (2.86640)
	Median	3.2154	2.8767	3.2373
	Q1-Q3	1.5056-5.0000	1.7544-4.7158	1.4821-5.2310
	Min-Max	-7.154-14.907	-4.108-10.788	-5.869-11.835
Week 78	n	247	122	122
	Mean (SD)	0.7699 (0.09238)	0.7887 (0.08610)	0.7757 (0.08769)
	Median	0.7690	0.7885	0.7870
	Q1-Q3	0.7060-0.8270	0.7350-0.8480	0.7180-0.8370
	Min-Max	0.539-1.082	0.560-1.118	0.557-0.965
% change from baseline	n	247	122	122
	Mean (SD)	3.8270 (3.28071)	4.0898 (2.96530)	3.9987 (3.33311)
	Median	3.7037	3.8512	4.0629
	Q1-Q3	1.9048-5.6164	2.0690-6.0150	2.0106-5.6845
	Min-Max	-9.240-15.528	-5.502-13.416	-6.214-14.188

- **Ancillary analyses**

Sensitivity analyses

Results of the tipping point analyses of the primary efficacy endpoint making estimated values worse up to a δ of -2% in any treatment arm in the MNAR imputation of missing Week 52 values not related to COVID-19 pandemic did not change study conclusion and supported the results of the primary endpoint analysis.

Results of the repeated primary endpoint analysis excluding subjects with forced randomization is provided in the table below.

Table 48. Repeated measures analysis of %CfB in LS-BMD at Week 52 to compare treatments excluding subjects with forced randomisation (TP1 FAS)

	No. of subjects			Adjusted mean change (SE)		Comparison of adjusted mean changes: Test vs Ref.		
Test vs Ref. (Comparison)	Test	Ref	Week	Test	Ref	Diff (Test-Ref)	SE	95% CI
GP2411 (N= 246) vs Prolia (N= 254)	246	254	52	4.956(0.2685)	5.129(0.2652)	-0.173	0.3362	(-0.833,0.488)

A mixed-model repeated measures analysis is performed for percentage change from baseline as the endpoint including the following variables: treatment (GP2411, Prolia), prior bisphosphonate use (yes, no), DXA machine type (Lunar, Hologic), visit (Week 26, Week 52), interaction between visit and treatment, and baseline LS-BMD value as a continuous covariate.
Missing data is assumed to be Missing At Random (MAR).

Results of the repeated analysis of %CfB in LS-BMD at Week 52 based on PPS to compare treatments using IRT strata are provided in the table below.

Table 49. Repeated measures analysis of %CfB in LS-BMD at Week 52 to compare treatments using IRT strata (PPS)

	No. of subjects			Adjusted mean change (SE)		Comparison of adjusted mean changes: Test vs Ref.		
Test vs Ref. (Comparison)	Test	Ref	Week	Test	Ref	Diff (Test-Ref)	SE	95% CI
GP2411 (N= 233) vs Prolia (N= 230)	233	230	52	4.960(0.2649)	5.104(0.2632)	-0.144	0.3327	(-0.798,0.510)

A mixed-model repeated measures analysis is performed for percentage change from baseline as the endpoint including the following variables: treatment (GP2411, Prolia), prior bisphosphonate use (yes, no), DXA machine type (Lunar, Hologic), visit (Week 26, Week 52), interaction between visit and treatment, and baseline LS-BMD value as a continuous covariate.

Results of the repeated analysis of %CfB in LS-BMD at Week 52 based on TP1 FAS to compare treatments using the stratification factors as derived from values stored in the clinical database are provided in the table below.

Table 50. Repeated measures analysis of %CfB in LS-BMD at Week 52 to compare treatments using actual treatment and database strata (TP1 FAS)

	No. of subjects			Adjusted mean change (SE)		Comparison of adjusted mean changes: Test vs Ref.		
Test vs Ref. (Comparison)	Test	Ref	Week	Test	Ref	Diff (Test-Ref)	SE	95% CI
GP2411 (N= 255) vs Prolia (N= 257)	255	257	52	4.977(0.2633)	5.160(0.2624)	-0.183	0.3328	(-0.837,0.470)

A mixed-model repeated measures analysis is performed for percentage change from baseline as the endpoint including the following variables: treatment (GP2411, Prolia), prior bisphosphonate use (yes, no), DXA machine type (Lunar, Hologic), visit (Week 26, Week 52), interaction between visit and treatment, and baseline LS-BMD value as a continuous covariate.
Missing data is assumed to be Missing At Random (MAR).

The efficacy primary endpoint analysis was repeated on modified PPS population as a sensitivity analysis. This modified PPS considered an update in two protocol deviations between the interim database and the final database leading to one additional exclusion and one additional inclusion into the PPS analysis. The results as presented in the table below.

Table 51. Repeated measures analysis of %CfB in LS-BMD at Week 52 to compare treatments (updated PPS)

	No. of subjects			Adjusted mean change (SE)		Comparison of adjusted mean changes: Test vs Ref.		
Test vs Ref. (Comparison)	Test	Ref	Week	Test	Ref	Diff (Test-Ref)	SE	95% CI
GP2411 (N= 234) vs Prolia (N= 229)	234	229	52	4.954(0.2629)	5.085(0.2620)	-0.130	0.3322	(-0.783,0.523)

A mixed-model repeated measures analysis is performed for percentage change from baseline as the endpoint including the following variables: treatment (GP2411, Prolia), prior bisphosphonate use (yes, no), DXA machine type (Lunar, Hologic), visit (Week 26, Week 52), interaction between visit and treatment, and baseline LS-BMD value as a continuous covariate.

- **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 52. Summary of Efficacy for trial CGP24112301

Title: A randomized, double-blind, multicenter integrated phase I/III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity of GP2411 (proposed denosumab biosimilar) and Prolia (EU-authorised)			
Study identifier	CGP24112301 EudraCT no. 2018-003523-11		
Design	International, multicenter, randomized, double-blind, two-arm, parallel-group study with a total duration of up to 83 weeks comprising two treatment phases (TPs): TP1 and TP2; primary efficacy assessment took place at the end of TP1 TP2 assessed the impact of a switch from Prolia to GP2411 on immunogenicity		
	Duration of run-in phase: Duration of main phase: Duration of extension phase:		not applicable ~52 weeks (TP1) ~26 weeks (TP2)
Hypothesis	Equivalence		
Treatments groups	TP1: GP2411		randomized patients: 263
	TP1: EU-Prolia		randomized patients: 264
	TP2: Continued GP2411 (GP2411/GP2411) Continued EU-Prolia (EU-Prolia/EU-Prolia) EU-Prolia/GP2411		2nd randomization at Week 52 continued patients: 253 re-randomized patients: 125
Efficacy endpoints and definitions	Primary endpoint	%CfB in LS-BMD at Week 52	Percent change from baseline (%CfB) in lumbar spine BMD (LS-BMD) at Week 52

	Secondary endpoints	%CfB in FN-BMD, TH-BMD at Week 52	%CfB in femoral neck BMD (FN-BMD) and total hip BMD (TH-BMD) at Week 52
	Secondary endpoints	%CfB in LS-BMD, FN-BMD, TH-BMD at Week 78	%CfB in LS-BMD, FN-BMD, TH-BMD at Week 78
Database lock	4-Jul-2022 (date of final DBL)		

Results and Analysis

Analysis description	**Primary analysis**			
Analysis population and time point description	Per-protocol Set (PPS) The PPS is the analysis set used for the efficacy analyses of the primary endpoint of %CfB in LS-BMD at Week 52. The PPS is characterized by the following criteria: • LS-BMD assessments at baseline and Week 52 are available • Subjects received treatment according to protocol at Day 1 and Week 26 • Subjects experienced no relevant protocol deviations which would affect LS-BMD up to Week 52			
Statistics and estimate variability	**Treatment group**	**GP2411**	**EU-Prolia**	**Comparison of adjusted means GP2411 vs EU-Prolia**
	Number of subjects (PPS)	233	230	
	Adjusted mean change in %CfB in **LS-BMD** at **Week 52**	4.955	5.099	Difference: -0.145
	Standard error	0.2634	0.2618	0.3325
	95% confidence interval			-0.798, 0.509
Analysis description:	**Secondary analysis**			
Analysis population and time point description	Per-protocol Set (PPS), Time point: Week 52			
Descriptive statistics and estimate variability	**Treatment group**	**GP2411**	**EU-Prolia**	
	Number of subjects (PPS)	233	229	
	Mean change in %CfB in **FN-BMD** at **Week 52**	2.4200	2.6157	
	Standard deviation	3.70552	3.26119	

	Number of subjects (PPS)	233	229	
	Mean change in %CfB in **TH-BMD** at **Week 52**	3.4289	3.3211	
	Standard deviation	2.71152	2.59266	
Analysis description	**Secondary analysis**			
Analysis population and time point description	TP2 Full Analysis Set (TP2 FAS), Time point: Week 78			
Descriptive statistics and estimate variability	**Treatment group**	**GP2411/ GP2411**	**EU-Prolia/ EU-Prolia**	**EU-Prolia/ GP2411**
	Number of subjects (TP2 FAS)	249	123	122
	Mean change in %CfB in **LS-BMD** at **Week 78**	6.8222	7.0694	6.4212
	Standard deviation	3.95225	4.72955	4.47102
	Number of subjects (TP2 FAS)	247	122	122
	Mean change in %CfB in **FN-BMD** at **Week 78**	3.2220	2.9406	2.6857
	Standard deviation	4.03733	3.92115	3.64193
	Number of subjects (TP2 FAS)	247	122	122
	Mean change in %CfB in **TH-BMD** at **Week 78**	3.8270	4.0898	3.9987
	Standard deviation	3.28071	2.96530	3.33311

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 CGP24112301 was a randomized, double-blind, multicentre, integrated phase I/III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity of GP2411 and EU-authorised Prolia. The study was conducted in 43 study centres in six countries (Bulgaria, Czech Republic, Japan, Poland, Spain and the United States). Subjects were randomized in a 1:1 ratio for the first treatment period (52 weeks). In the second treatment period (week 52-78) subjects receiving EU-Prolia were re-randomised to receive either GP2411 or EU-Prolia. The subjects received in total three s.c. doses of GP2411 or EU-Prolia. Overall, the design of study CGP24112301 is acceptable and is generally in agreement with previous Scientific Advice received from EMA (EMEA/H/SA/3409/1/2016/III, EMEA/H/SA/3409/2/2017/III, EMEA/H/SA/3409/2/FU/1/2018/III and EMA/SA/0000067538).

For study CGP24112301, a population consisting of postmenopausal women with a diagnosis of osteoporosis was selected. Overall, the inclusion and exclusion criteria are considered appropriate for recruitment of a population consisting of postmenopausal women with a diagnosis of osteoporosis.

The dose, frequency, and route of administration of the test and reference product were according to the SmPC of Prolia, which is considered acceptable.

The Applicant had different primary and secondary objectives for various health authorities, which is acceptable. For the EMA, the primary objectives of Study CGP24112301 were the demonstration of similar PD in terms of the bone resorption marker CTX and similar efficacy in terms of BMD between GP2411 and EU-Prolia. The secondary objectives included PK, PD, efficacy, safety and immunogenicity aspects of GP2411 and the reference product. The objectives also included an evaluation of PK, PD, efficacy, safety and immunogenicity aspects after a transition of subjects from Prolia to GP2411. Overall, the objectives of the study are endorsed.

The co-primary endpoints of the study were the "Percent change from baseline (%CfB) in lumbar spine BMD (LS-BMD) at Week 52" and the "AUEC after first dose of %CfB in serum CTX". The choice of the primary endpoints was intensively discussed during the previous EMA-SA procedures (EMEA/H/SA/3409/1/2016/III, EMEA/H/SA/3409/2/2017/III, EMEA/H/SA/3409/2/FU/1/2018/III and EMA/SA/0000067538) and are in line with the recommendations from the EMA. BMD is a quantitative predictor of osteoporotic fractures in postmenopausal women without a previous fracture. However, the causal link (surrogacy) between the marker and longer-term endpoints has not been unequivocally proven. (Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis, CPMP/EWP/552/95 Rev. 2). After denosumab treatment, the changes in BMD are slow and modest, while the changes in sCTX are large and dynamic. Thus, sCTX might be more sensitive to compare test and reference product in terms of biosimilarity, however, the clinical relevance might be higher for BMD, which is often used in clinical trials. Thus, the choice of these

endpoints as co-primary endpoints for study CGP24112301 is considered appropriate for the assessment of biosimilarity of GP2411 and EU-Prolia.

For the %CfB in LS-BMD at Week 52, to fulfil the equivalence criteria, the 95% CI for the difference in means had to be contained within the pre-specified margin of [-1.45%, 1.45%]. The Applicant based the derivation of the margin on three published clinical trials and the retention of treatment effect. According to the applicant, a margin of 1.45% retains at least 70% of the minimum treatment effect. Of note, this approach was recommended by CHMP in a follow-up Scientific advice (EMA/SA/0000067538) and is thereby accepted. The 95% confidence limits (-0.796%; 0.509%) are very well within the pre-defined and accepted equivalence range and estimate a 'maximum' difference of 0.796%. This size of a difference between the treatments is thereby convincingly supporting clinical equivalence of the treatments.

The Applicant chose to base the assessment of PD similarity upon the 95% CIs of the ratio of the geometric means (test/reference) for the AUEC of %CfB in serum CTX concentrations, which had to be contained entirely within the pre-specified acceptance margin of [0.8000, 1.2500]. The 95% confidence limits (0.98; 1.01) were close enough to 1 and estimate a 'maximum' difference of 2%. This size of a difference between the treatments is considered clinically not relevant and is thereby convincingly supporting equivalence of the treatments. No further justification on the predefined equivalence range is needed.

Of note, the results of the co-primary endpoint "AUEC after first dose of %CfB in serum CTX" are discussed in the pharmacology section (3.3.2) while the results of the co-primary endpoint "Percent change from baseline in LS-BMD at Week 52" are discussed further below in the section "Efficacy data and additional analyses".

The secondary efficacy endpoints included investigation of BMD at the lumbar spine, femoral neck, and total hip at different time-points. The secondary PD endpoints consisted of "CTX and PINP serum concentrations as per visit schedule up to Week 52". The secondary PK endpoints in this study were the "Serum PK parameters AUCinf and Cmax after the first dose" and "Denosumab serum concentrations as per visit schedule up to Week 52". The secondary endpoints are all acceptable. Nevertheless, apart from the described primary and secondary endpoints, the applicant was also asked to comparatively analyse the classical AUC under the sCTX-effect curve (0-t), and to display the estimated ratio of geometric means together with 95% cIs. The Applicant provided the requested data for the classical AUC(0-t) under the sCTX-effect curve. The point estimate was 0.98 with the 95% CI being (0.94, 1.03). Thus, these results support the primary AUEC analysis.

The protocol of the study was amended six times. The Applicant provided a detailed overview of the protocol amendments and provided all relevant protocol versions. All amendments happened prior to study unblinding. The protocol amendments are regarded appropriate.

The sample size was updated in Protocol version 6 and was reduced from 522 to 496 subject on 21 Feb 2020 after more than 200 patients had already been recruited. In this update, the drop-out rate was decreased from 25% to 15% and the SD estimate of %CfB in LS-BMD at Week 52 was updated from 3.96 to 4.08 derived as pooled SD over the 3 historical published trials. Because of this minor reduction in sample size and in light of the results lying clearly close to unity, no need is seen to clarify sample size update post-hoc.

On day 1, subjects were randomized in a 1:1 ratio to one of the two treatments groups GP2411 or EU-Prolia. After 52 weeks, subjects in the EU-Prolia group were re-randomized in a 1:1 ratio to further receive EU-Prolia or switch to GP2411. Subjects in the initial GP2411 group continued their initial treatment. The process of randomization was adequately described and is considered acceptable. A subject randomization list was also provided, which is endorsed.

Study CGP24112301 was a double-blind study, with subjects and investigators being blinded throughout the study. However, the appearance of the GP2411 and EU-Prolia syringes differed and therefore, the staff handling and administering the study drug was unblinded. In order to keep the blinding of the subjects, they were asked to wear a blindfold during the injections, or a screen was used. The unblinded study staff did not perform any clinical assessments. The process of blinding was adequately described and is considered acceptable.

The definitions of the analysis sets are acknowledged. The definition of the TP1 FAS seems restricted by requiring at least one post-baseline LS-BMD-value. However, at least 97% of randomised patients in each treatment group were included in the TP1 FAS and therefore, no issue is raised.

Concerning primary and secondary analyses, the use of an MMRM model for the endpoint %CfB in LS-BMD as well as the use of ANCOVA models for AUEC of %CfB in serum CTX concentrations and PK parameters (AUCinf and Cmax) are endorsed. However, against the recommendation in the EMA *Guideline on adjustment for baseline covariates in clinical trials*, not all stratification factors used during randomisation were included in the models. Although the applicant justified their omission, extended models including all stratification factors should be run for all endpoints in a per-protocol and an intention-to-treat set, in order to confirm the robustness of the results for this biosimilarity assessment. Moreover, the factor DX machine type was pre-specified to be included in the model for %CfB in LS-BMD, but since a percentage change was the endpoint, its influence should be minor. Therefore, a sensitivity analysis where this factor is excluded should be performed to prove its negligible impact. Anyway, analysis by the CHMP based on submitted raw data ruled out the concerns about in/exclusion of DX machine type and stratification factors since all analyses performed led to the same conclusions supporting clinical equivalence. To complement sensitivity analyses, the pre-defined tipping point analysis for the primary endpoint %CfB in LS-BMD in the TP1 FAS assessing the robustness of MAR assumption was asked to be repeated by the applicant with an extended model including all stratification factors except region. In particular, the model should include treatment, time, time*treatment, baseline BMD, DX machine type, and all stratification factors except region. The applicant provided the additional sensitivity analyses. The results of the additional tipping point analysis showed that the results are robust up to a deviation of -2% from the imputed values. The point estimate as well as the estimated standard deviation were stable and the confidence intervals were contained in the equivalence margin for all investigated deviations.

The participant flow is described in sufficient detail and is comprehensible. The number of subjects completing the study was high. In addition, the number of subjects discontinuing the study and reasons for discontinuation were similar between the groups. The number of subjects with at least one protocol deviation during TP1 was 256. There were slightly more subjects in the EU-Prolia group (136 subjects) having a protocol deviation than in the GP2411 group (120 subjects). The use of "prohibited concomitant medication" was quite high in both groups (5.7% in the GP2411 group and 6.8% in the EU-Prolia group) and this protocol deviations also led to exclusion from the PPS and PDS analysis sets. The number of subjects excluded from the PDS set was 35 in the GP2411 group and 51 in the EU-Prolia group. Thus, there is an imbalance in the subjects excluded from the PDS set. The most common reason for exclusion from PDS was the protocol deviation "prohibited concomitant medication". Besides the protocol deviations, there were further reasons to exclude subjects from the PDS set that were mainly related to the timing of the sample collection or the evaluability of the sample. The imbalance in subjects excluded from the PDS set (13.3% excluded in the GP2411 group and 19.3% excluded in the EU-Prolia group) was mainly driven by the reason "required visit samples are missing or excluded" (5.3% in the GP2411 group and 10.2% in the EU-Prolia group). Detailed listing shows that the reason "Visit 2 concentration non-fasting or time window violation" is responsible for the imbalance between the groups (GP2411: 1.5% and EU-Prolia: 6.4%). The Applicant was asked to provide

a possible explanation for this imbalance and provide further details on the time window violations. The Applicant could not provide an explanation for the imbalance at visit 2 but noted that visit 2 occurred prior to the double-blind scheduled treatment was given and therefore no link to randomized treatment assignment can be made. Thus, the applicant considers it a chance finding. In addition, the applicant provided the requested details on the time window violations for the whole study. The total number of subjects with time window or fasting violations was 14 in the GP2411 group and 22 in the Prolia group. Based on sample level, the frequency of deviations was low (0.7% of 1807 GP2411 samples and 1.2% of 1800 EU-Prolia samples). The median time deviations from the allowed time window was 30 min for the GP2411 samples and 30 min for the EU-Prolia samples. In conclusion, the applicant provided the requested data and it is agreed that the imbalance between groups in the time window violations at visit 2 might indeed be a chance finding.

Overall, the demographics and baseline characteristics were well balanced between the GP2411 and EU-Prolia group for the SAF set in treatment period 1. The Applicant also provided an overview of the baseline characteristics for treatment period 1 for the different analysis sets (FAS, PPS, PKS and PDS) and for the subjects enrolled before and during the COVID-19 pandemic. In all these sets, the baseline characteristics were well balanced between the GP2411 and EU-Prolia group and no concerns arise. The same holds true for a comparison of the demographics and baseline characteristics among the groups for treatment period 2. This is appropriate.

The baseline disease characteristics were also balanced between the GP2411 and EU-Prolia groups for the SAF set in the treatment period 1. In addition, the baseline disease characteristics were also provided for treatment period 1 for the different analysis sets (FAS, PPS, PKS and PDS) and for the subjects enrolled before and during the COVID-19 pandemic. In all these sets, the baseline disease characteristics were well balanced between the GP2411 and EU-Prolia group and no concerns arise. The same holds true for a comparison of the baseline disease characteristics among the groups for treatment period 2. This is endorsed.

The medical history and concurrent illnesses, as well as the prior and concomitant medication were also provided by treatment group and treatment period. There was a concern regarding a table of the CSR in which the relevant medical histories and current medical conditions are listed for the TP1 SAF set. In the table, it is stated that osteoporosis is present in only 28.1% of the GP2411 group and 31.1% of the EU-Prolia group. In addition, menopause and post-menopause apply to only 8.4% and 3.4% of the GP2411 group, respectively, and to 12.1% and 4.2% of the EU-Prolia group. It was counterintuitive why in a recruited population of postmenopausal women with a diagnosis of osteoporosis these conditions are not applying to 100% of the subjects. The Applicant was asked to clarify. The Applicant confirmed that in line with the inclusion criteria 2 and 5, all subjects enrolled in study 301 were post-menopausal women with osteoporosis. The discrepancy in the abovementioned table of the CSR was due to data erroneously entered on the Medical History CRF page for some subjects. Although the CRF Completion Guidelines instructed investigators not to enter the diagnosis or symptoms under investigation or any condition related to menopause/post-menopause, some investigators did not follow these guidelines. The explanation provided by the applicant is regarded adequate.

Efficacy data and additional analyses

The %CfB in LS-BMD at Week 52 was 4.955% for the GP2411 group and 5.099% for the EU-Prolia group. This is in a range that would have been expected from the Prolia registrational studies. The primary efficacy analysis for EMA was performed on the PPS set and revealed that the difference between the GP2411 and the EU-Prolia group was -0.145% with the corresponding 95% CI being -0.796% and 0.509%. Thus, the primary efficacy endpoint was met supporting the biosimilarity of GP2411 and EU-Prolia in terms of efficacy. The 95%

confidence limits (-0.796%; 0.509%) are very well within the pre-defined and accepted equivalence range of [-1.45%, 1.45%] and estimate a 'maximum' difference of 0.796%. This size of a difference between the treatments is thereby convincingly supporting clinical equivalence of the treatments. Additionally, the primary efficacy endpoint analysis was also conducted with the TP1 FAS set. The results of this analysis support the primary efficacy analysis in the PPS set, as the 95% cIs of the adjusted mean difference of %CfB in LS-BMD was within the pre-specified margin. Moreover, the applicant provided several sensitivity analyses which also support the primary efficacy endpoint analysis.

Of note, the results of the co-primary endpoint "AUEC after first dose of %CfB in serum CTX" are discussed in the clinical pharmacology section.

The secondary efficacy endpoints included the %CfB in BMD at lumbar spine at week 26. The summary statistics for LS-BMD for the PPS set showed that the mean LS-BMD at week 26 and the %CfB was similar for both groups, supporting the primary endpoint analysis. The mean LS-BMD at week 26 was 0.7770 g/cm3 for the GP2411 group and 0.7777 g/cm3 for the EU-Prolia group. The %CfB at week 26 was 3.65% for the GP2411 group and 3.67% for the EU-Prolia group.

Additionally, the secondary efficacy endpoints included the %CfB in BMD at femoral neck and %CfB in BMD at total hip, both at week 26 and week 52. The summary statistics for FN-BMD and TH-BMD showed comparable mean BMD and %CfB between the GP2411 and EU-Prolia group, respectively. This held true both for the week 26 and week 52 comparison, thus further supporting the efficacy data derived from the LS-BMD.

In addition, the applicant provided week 78 data for the LS-BMD, FN-BMD and TH-BMD, after the TP1 EU-Prolia group was split into either receiving a further dose of EU-Prolia or GP2411 for the TP2. The initial GP2411 group received one further dose of GP2411 in TP2. The week 78 results for the TP2 FAS set showed that the switch from Prolia to GP2411 does not seem to cause any difference in terms of LS-BMD, FN-BMD or TH-BMD compared to staying on the same product. The mean LS-BMD at week 78 was 0.8010 g/cm3, 0.8026 g/cm3 and 0.7952 g/cm3 for the GP2411/GP2411, the EU-Prolia/EU-Prolia and the EU-Prolia/GP2411 group, respectively. The %CfB at week 78 was 6.82% for the GP2411/GP2411group, 7.07% for the EU-Prolia/EU-Prolia group and 6.42% for the EU-Prolia/GP2411 group. Furthermore, for the mean FN-BMD and TH-BMD at week 78, comparable results among the groups were seen.

2.6.7. Conclusions on the clinical efficacy

In study CGP24112301, the primary efficacy analysis based on the %CfB in LS-BMD at Week 52 was met as the 95% CI of the difference between the Jubbonti and the EU-Prolia group was within the pre-specified equivalence criteria. This was further supported by secondary endpoint and sensitivity analyses. Thus, the provided efficacy data support the biosimilarity of Jubbonti and EU-Prolia.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Exposure data are available for the following studies and populations:

Study 101: Healthy male subjects received a single s.c. injection of 35 mg (fixed dosing volume of 0.5 mL) GP2411 or EU-Xgeva or US-Xgeva. Dose adjustments were not allowed and did not occur. The total study

duration was 39 weeks. The SAF consisted of all 499 treated subjects (GP2411: 166 subjects; EU-Xgeva: 171 subjects; US-Xgeva: 162 subjects).

Study 301: Female subjects with PMO initially received two 60 mg s.c. injections by PFS of GP2411 or EU-Prolia at 26-week intervals during TP1. At Week 52, all subjects in the GP2411 group continued treatment with a third dose of GP2411. Subjects who had received EU-Prolia during TP1 were re-randomized in a 1:1 ratio to either continue treatment with a third dose of EU-Prolia or switch to GP2411 during TP2. The total study duration was 78 weeks, including a 26-week follow-up after the last dose. The TP1 SAF consisted of all 527 randomized subjects treated in TP1. The TP2 SAF consisted of 502 subjects treated in TP2.

Similar proportions of subjects in both treatment groups received both scheduled s.c. doses of 60 mg GP2411 (97%) or EU-Prolia (96.6%) in TP1 and the duration of exposure was similar between treatment groups.

The administration of the third dose was part of TP2; all subjects who entered TP2 received the third dose. For TP2, 124 subjects in the EU-Prolia group were switched to GP2411 and received GP2411 as a third dose, whereas 253 and 125 subjects remained on GP2411 and EU-Prolia, respectively.

Subject disposition

Study 101: A total of 502 subjects were randomized in a 1:1:1 ratio to the treatment arms GP2411, EU-Xgeva, and US-Xgeva. Similar proportions of subjects completed the study. The most common reason for discontinuation of study participation was 'Subject decision', with 2 subjects each in the GP2411 and US-Xgeva groups. Overall only one subject (in the GP2411 group) discontinued due to an adverse event.

Study 301: A total of 527 subjects were randomized (GP2411: 263 subjects; EU-Prolia: 264 subjects). The number of subjects who discontinued early (prior to finalizing TP1) was similar in both treatment groups (3.8% for GP2411 and 5.7% for EU-Prolia).

The most common reason for premature study discontinuation was 'Subject decision'. The death of one subject in the GP2411 group was considered unrelated to study drug (see further below for details).

A total of 502 subjects entered TP2, of which 253 subjects continued on GP2411, 125 subjects continued on EU-Prolia, and 124 subjects switched from EU-Prolia to GP2411. Two subjects discontinued early (prior to finalizing TP2); both discontinuations were in the continued EU-Prolia group. There were no premature discontinuations due to aEs during TP2.

Table 53.Study 301 – Subject disposition – TP2 (TP2 RAS)

Disposition/Reason	GP2411/GP2411 N=253 n (%)	EU-Prolia/EU-Prolia N=125 n (%)	EU-Prolia/GP2411 N=124 n (%)
Re-randomized subjects	253 (100)	125 (100)	124 (100)
Treated in TP2	253 (100)	125 (100)	124 (100)
Completed TP2	253 (100)	123 (98.4)	124 (100)
Discontinued from study in TP2	0	2 (1.6)	0
Reason for discontinuation			
Lost to follow-up	0	1 (0.8)	0
Subject decision	0	1 (0.8)	0

Demographics and baseline characteristics

The demographics and baseline characteristics of Studies 101 and 301 are described above in the pharmacology and efficacy section, respectively.

Disease-specific baseline characteristics in the study population (female subjects with PMO) were similar between both treatment groups (GP2411 and EU-Prolia). The key baseline disease characteristics (assessed at study entry) were also comparable after re-randomization across the three TP2 treatment groups.

However, imbalances are noted in the percentage of subjects between groups in the TP1 SAF set with regards to relevant medical histories and current medical conditions as outlined in the discussion section.

The frequency and pattern of use of concomitant medications (i.e., taken after study treatment) were similar across treatment groups (GP2411, EU-Xgeva, US-Xgeva) in Study 101. The most frequently reported concomitant medications were mineral supplements and vitamins followed by vaccines (mainly against SARS-CoV-2).

There were no meaningful differences in the frequency and pattern of use of concomitant medications across the three treatment groups (GP2411/GP2411, EU-Prolia/EU-Prolia, and EU-Prolia/GP2411) in Study 301. The most frequently reported concomitant medications were calcium and vitamin D supplements, lipid modifying agents, and agents acting on the renin-angiotensin system.

2.6.8.2. Adverse events

In the following sections, only treatment-emergent aEs are presented i.e., defined as any AE that started after administration of study drug or an event that was present prior to administration of study drug but increased in severity afterwards. If it was unclear from the onset date if the event onset was prior to dosing at Day 1 (Visit 3 in Study 101 and Visit 2 in Study 301), then the AE was considered treatment-emergent.

In Study 301, aEs with an onset date (and time) from Day 1 up until dosing on Visit 15 were assigned to TP1. aEs with an onset date (and time) after dosing at Visit 15 were assigned to TP2. In cases where it was unclear from the onset date (and time) if the onset was prior to dosing at Visit 15, then the AE was assigned to both TP1 and TP2 but was only to be counted once in the combined TP1 and TP2 analysis. aEs are presented by TP1, TP2, and overall for TP1 and TP2 combined for Study 301.

In both studies, aEs were summarized by the number (and percentage) of subjects reporting any TEAE, by treatment and by MedDRA SOC and PT. aEs were coded using MedDRA version 25.0 in both studies. The severity of aEs and ISRs were graded using CTCAE version 5.0 in both studies.

In both studies, positive results of RT-PCR tests for SARS-CoV-2 were reported as AE 'confirmed COVID-19' (verbatim term). If a subject reported signs and symptoms possibly caused by SARS-CoV-2 but was not tested with an RT-PCR test, the case had to be documented as 'suspected COVID-19'. If the subject was tested, but a COVID-19 infection was not confirmed, the investigator could document signs and symptoms in the eCRF or a different diagnosis as AE or still report the case as 'suspected COVID-19' as per their judgement.

<u>Study 101 in healthy male subjects</u>

The overall incidence of aEs was similar across treatment groups. There were no deaths in the study.

The proportion of subjects with at least one AE was similar across treatment groups, for all grades as well as grade 3 or 4.

Incidences for aEs reported within specific SOCs were, in general, similar across treatment groups. The SOC with the highest incidence of aEs was Infections and infestations, mainly due to nasopharyngitis and COVID-19 cases.

Also on the PT level, incidences were in general similar across treatment groups. The most frequently reported AE was headache.

Table 54. Study 101-- aEs regardless of study drug relationship by SOC and PT (at least 2% of subjects in any treatment group) (SAF)

	GP2411 N=166		Xgeva-EU N=171		Xgeva-US N=162	
Primary SOC PT	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)
Number of subjects with at least one TEAE	**121 (72.9)**	**2 (1.2)**	**130 (76.0)**	**3 (1.8)**	**115 (71.0)**	**2 (1.2)**
Infections and infestations	57 (34.3)	0	59 (34.5)	1 (0.6)	40 (24.7)	0
COVID-19	18 (10.8)	0	17 (9.9)	0	20 (12.3)	0
Nasopharyngitis	17 (10.2)	0	30 (17.5)	0	12 (7.4)	0
Rhinitis	7 (4.2)	0	6 (3.5)	0	5 (3.1)	0
Suspected COVID-19	6 (3.6)	0	8 (4.7)	0	2 (1.2)	0
Nervous system disorders	44 (26.5)	1 (0.6)	39 (22.8)	1 (0.6)	26 (16.0)	0
Headache	38 (22.9)	0	38 (22.2)	1 (0.6)	19 (11.7)	0
Musculoskeletal and connective tissue disorders	33 (19.9)	0	36 (21.1)	0	39 (24.1)	1 (0.6)
Back pain	13 (7.8)	0	14 (8.2)	0	13 (8.0)	0
Arthralgia	11 (6.6)	0	10 (5.8)	0	6 (3.7)	0
Pain in extremity	5 (3.0)	0	4 (2.3)	0	3 (1.9)	0
Gastrointestinal disorders	28 (16.9)	1 (0.6)	28 (16.4)	0	28 (17.3)	0
Diarrhoea	10 (6.0)	0	6 (3.5)	0	8 (4.9)	0
Toothache	5 (3.0)	0	3 (1.8)	0	4 (2.5)	0
Abdominal pain	2 (1.2)	0	4 (2.3)	0	2 (1.2)	0
Abdominal discomfort	1 (0.6)	0	2 (1.2)	0	4 (2.5)	0
General disorders and administration site conditions	19 (11.4)	0	17 (9.9)	0	10 (6.2)	0
Fatigue	6 (3.6)	0	6 (3.5)	0	2 (1.2)	0
Chills	4 (2.4)	0	1 (0.6)	0	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders	15 (9.0)	0	15 (8.8)	0	6 (3.7)	0
Cough	7 (4.2)	0	5 (2.9)	0	1 (0.6)	0
Oropharyngeal pain	5 (3.0)	0	6 (3.5)	0	4 (2.5)	0
Injury, poisoning and procedural complications	14 (8.4)	0	17 (9.9)	0	21 (13.0)	0
Ligament sprain	4 (2.4)	0	1 (0.6)	0	4 (2.5)	0
Metabolism and nutrition disorders	14 (8.4)	0	13 (7.6)	0	18 (11.1)	0
Hypocalcaemia	14 (8.4)	0	11 (6.4)	0	17 (10.5)	0
Skin and subcutaneous tissue disorders	11 (6.6)	0	11 (6.4)	0	5 (3.1)	0
Erythema	0	0	4 (2.3)	0	1 (0.6)	0
Immune system disorders	8 (4.8)	0	13 (7.6)	0	15 (9.3)	0
Immunisation reaction	8 (4.8)	0	11 (6.4)	0	15 (9.3)	0
Psychiatric disorders	3 (1.8)	0	4 (2.3)	1 (0.6)	1 (0.6)	0

Numbers (n) represent counts of subjects. A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.0, CTCAE version 5.0

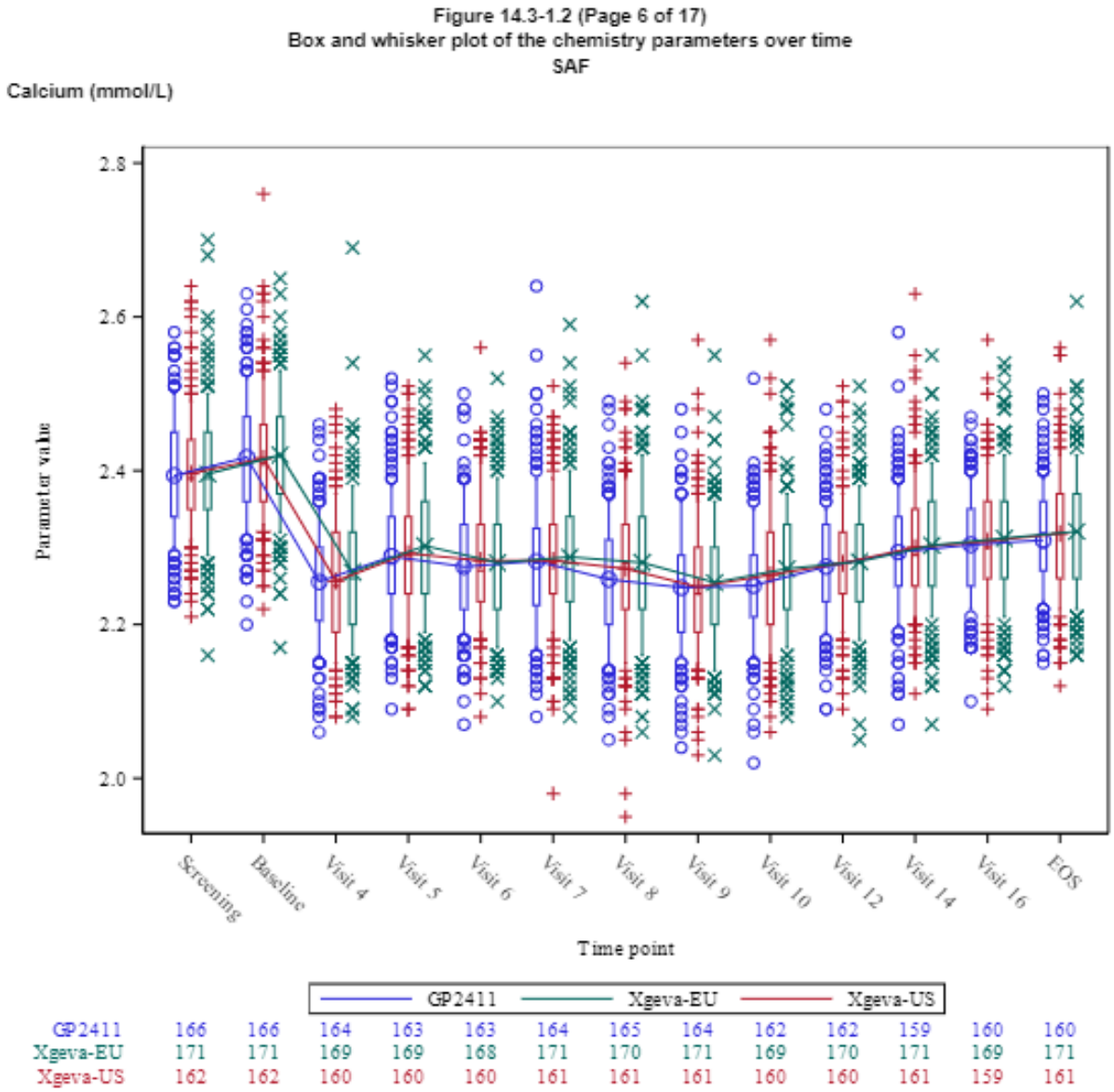
Higher incidences (i.e. imbalance of >5%) on SOC level could be seen in the GP2411 group compared to the US-Xgeva group for the SOCs Infections and infestations, Nervous system disorders, Respiratory, thoracic and mediastinal disorders, and General disorders and administration site conditions. However, these imbalances were not considered clinically meaningful as these were driven by a few aEs reported by a low number of subjects. It should also be noted that the incidences were similar between GP2411 and EU-Xgeva for these SOCs.

Imbalances of >5% on PT level could be seen for the events headache and nasopharyngitis, but these were not considered clinically meaningful. The event headache occurred with a similar incidence in the GP2411 and EU-Xgeva group, but with a higher incidence in the GP2411 group (and EU-Xgeva group) than in the US-Xgeva group. The imbalance between the GP2411 and US-Xgeva groups was mainly driven by events of grade 1 while the incidence of grade 2 events was similar between these 2 treatment groups. The only event of grade 3 headache occurred in the EU-Xgeva group.

The event nasopharyngitis occurred with a higher incidence in the EU-Xgeva group than in the GP2411 and US-Xgeva groups. All events were of grade 1 or 2.

A known adverse reaction for Xgeva is hypocalcaemia. In this study, calcium levels <2.10 mmol/L were documented as aEs of hypocalcaemia, irrespective of clinical significance. Such events occurred with similar incidences across treatment groups. Most events were of grade 1 severity; 2 subjects in the US-Xgeva group experienced events of grade 2 and no events of grade 3 or 4 occurred. Calcium levels over time are depicted in the following figure. The incidence of hypocalcaemia was in line with the safety profile of Xgeva (Xgeva SmPC and Xgeva USPI).

Figure 10. Calcium levels over time (Study CGP24112101, SAF)



The overall incidence of aEs suspected to be related to study drug by the investigator was similar across treatment groups. None of the aEs suspected to be related to study medication was of grade 3 or 4.

Table 55. TEAEs suspected to be related to study medication by system organ class and preferred term (at least 2% of subjects in any treatment group) (SAF)

	GP2411 N=166		Xgeva-EU N=171		Xgeva-US N=162	
Primary SOC PT	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)
Number of subjects with at least one related TEAE	49 (29.5)	0	47 (27.5)	0	40 (24.7)	0
Nervous system disorders	20 (12.0)	0	18 (10.5)	0	10 (6.2)	0
Headache	17 (10.2)	0	16 (9.4)	0	8 (4.9)	0
Metabolism and nutrition disorders	13 (7.8)	0	9 (5.3)	0	15 (9.3)	0
Hypocalcaemia	13 (7.8)	0	9 (5.3)	0	15 (9.3)	0
Musculoskeletal and connective tissue disorders	11 (6.6)	0	10 (5.8)	0	7 (4.3)	0
Back pain	3 (1.8)	0	4 (2.3)	0	0	0
Gastrointestinal disorders	6 (3.6)	0	4 (2.3)	0	4 (2.5)	0
General disorders and administration site conditions	3 (1.8)	0	6 (3.5)	0	3 (1.9)	0

Numbers (n) represent counts of subjects. A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.0, CTCAE version 5.0.

The most frequent AE with a suspected causal relationship was headache in all treatment groups (GP2411: 17 subjects, 10.2%; EU-Xgeva: 16 subjects, 9.4%; US-Xgeva: 8 subjects, 4.9%).

Imbalances of >5% could be seen in the GP2411 group compared to the Xgeva-US group for the SOC Nervous system disorders and the event headache, but these were not considered clinically meaningful for the following reasons. The imbalance in the SOC was driven by the imbalance in the event headache and by events reported by 1 or 2 subjects in the GP2411 groups. The imbalance in the event headache was mainly driven by grade 1 events, while the number of subjects with grade 2 events was similar between both treatment groups. It should be also noted that the incidences were similar between GP2411 and Xgeva-EU in this SOC and for the event headache. The imbalances need to be interpreted in the light of the overall low incidence of events in each treatment group in this SOC and for the event headache which should be taken into consideration when interpreting the data.

Overall, the majority of aEs was grade 1 or 2 in all treatment groups.

A total of 7 subjects experienced aEs of grade 3: 2 (1.2%) subjects in the GP2411 group, 3 (1.8%) subjects in the EU-Xgeva group, and 2 (1.2%) subjects in the US-Xgeva group. None of the grade 3 aEs were suspected to be related to the study medication by the investigator ([5.3.3.1-101-Listing 16.2.7-1]).

No subject experienced aEs of grades 4 and 5 in the study.

Study 301 in female subjects with PMO

Treatment period 1 (Day 1 to Week 52)

The overall incidence of aEs was similar in the GP2411 and EU-Prolia treatment groups.

Table 56. Overview of adverse events, TP1 (TP1 SAF)

	GP2411 (N=263)		EU-Prolia (N=264)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Category	n (%)	n (%)	n (%)	n (%)
Number of subjects with at least one TEAE	157 (59.7)	13 (4.9)	181 (68.6)	10 (3.8)
Treatment-related	36 (13.7)	0	49 (18.6)	0
Number of subjects with at least one				
Serious TEAE	12 (4.6)	9 (3.4)	8 (3.0)	5 (1.9)
Treatment-related	0	0	0	0
Fatal serious TEAE	1 (0.4)	0[a]	0	0
Treatment-related	0	0	0	0
TEAE leading to study drug discontinuation[b]	1 (0.4)	1 (0.4)	4 (1.5)	3 (1.1)
Treatment-related	0	0	0	0
TEAE leading to study discontinuation[b]	3 (1.1)	1 (0.4)	3 (1.1)	2 (0.8)
Treatment-related	0	0	0	0

Numbers (n) represent counts of subjects. A subject with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 25.0, CTCAE version 5.0.
[a] fatal TEAE (death) = grade 5
[b] See Section 9.4.7 for details on study discontinuation and study drug discontinuation.

One subject in the GP2411 group died during the study, cause of death unknown; however, there was no suspected causal relationship to study drug (see below).

The incidence of the most frequent aEs (occurring in at least 3% of subjects in any treatment group) by SOC and PT were similar between both treatment groups during TP1 for all grades as well as for grades 3 or 4.

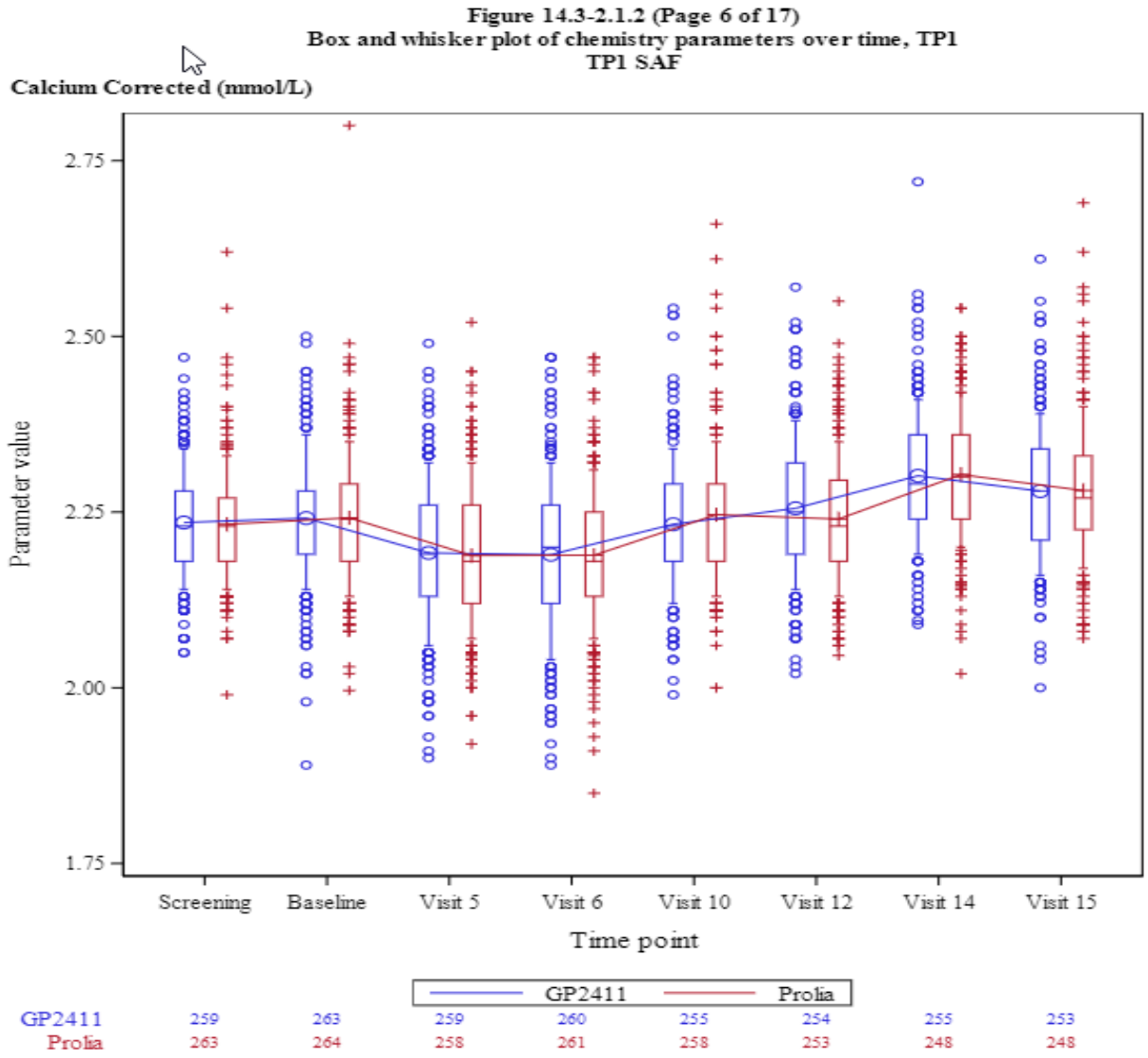
Table 57. Study 301–- aEs, regardless of study drug relationship, by primary SOC and PT (in at least 3% of subjects in any treatment group), TP1 (TP1 SAF)

	GP2411 N=263		EU-Prolia N=264	
Primary system organ class Preferred term	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)
Number of subjects with at least one TEAE	157 (59.7)	13 (4.9)	181 (68.6)	10 (3.8)
Infections and infestations	64 (24.3)	1 (0.4)	76 (28.8)	4 (1.5)
Nasopharyngitis	23 (8.7)	0	16 (6.1)	0
COVID-19	10 (3.8)	1 (0.4)	14 (5.3)	1 (0.4)
Urinary tract infection	5 (1.9)	0	10 (3.8)	0
Upper respiratory tract infection	4 (1.5)	0	8 (3.0)	0
Cystitis	1 (0.4)	0	9 (3.4)	0
Musculoskeletal and connective tissue disorders	52 (19.8)	1 (0.4)	50 (18.9)	1 (0.4)
Arthralgia	12 (4.6)	0	8 (3.0)	0
Back pain	10 (3.8)	1 (0.4)	9 (3.4)	1 (0.4)
Spinal osteoarthritis	4 (1.5)	0	9 (3.4)	0
Metabolism and nutrition disorders	42 (16.0)	0	44 (16.7)	0
Hypocalcaemia	28 (10.6)	0	26 (9.8)	0
Vitamin D deficiency	7 (2.7)	0	12 (4.5)	0
Gastrointestinal disorders	37 (14.1)	2 (0.8)	42 (15.9)	1 (0.4)
General disorders and administration site conditions	22 (8.4)	0	22 (8.3)	0
Injection site reaction	7 (2.7)	0	10 (3.8)	0
Nervous system disorders	17 (6.5)	0	26 (9.8)	0
Headache	6 (2.3)	0	13 (4.9)	0
Injury, poisoning and procedural complications	16 (6.1)	5 (1.9)	19 (7.2)	0
Investigations	11 (4.2)	2 (0.8)	7 (2.7)	0
Skin and subcutaneous tissue disorders	11 (4.2)	1 (0.4)	17 (6.4)	0
Vascular disorders	10 (3.8)	1 (0.4)	6 (2.3)	0

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.0, CTCAE version 5.0.
Source: 5.3.5.1-301-Table 12-3

The most frequently reported AE by PT was hypocalcaemia occurring with similar incidences in both treatment groups. All cases of hypocalcaemia were grade 1 (GP2411: 18; EU-Prolia: 22) or grade 2 (GP2411: 10; EU-Prolia: 4). None of the subjects showed clinical symptoms associated with hypocalcaemia. Calcium levels over time are depicted in the following figure.

Figure 11. Calcium levels over time (Study CGP24112301, TP1 SAF)



The overall incidence of aEs with a suspected causal relationship to study drug was similar between the two treatment groups, and all were of grade 1 or 2 severity.

Table 58. Related aEs, by SOC and PT, TP1 (TP1 SAF)

Primary system organ class Preferred term	GP2411 (N=263)		EU-Prolia (N=264)	
	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)
Subjects with at least one related TEAE	36 (13.7)	0	49 (18.6)	0
Metabolism and nutrition disorders	21 (8.0)	0	25 (9.5)	0
Hypocalcaemia	21 (8.0)	0	24 (9.1)	0
Vitamin D deficiency	0	0	1 (0.4)	0
General disorders and administration site conditions	8 (3.0)	0	12 (4.5)	0
Injection site reaction	7 (2.7)	0	10 (3.8)	0
Malaise	1 (0.4)	0	0	0
Swelling	1 (0.4)	0	0	0
Pyrexia	0	0	2 (0.8)	0
Musculoskeletal and connective tissue disorders	4 (1.5)	0	7 (2.7)	0
Arthralgia	3 (1.1)	0	2 (0.8)	0
Myalgia	1 (0.4)	0	1 (0.4)	0
Pain in extremity	1 (0.4)	0	0	0
Bone pain	0	0	1 (0.4)	0
Joint swelling	0	0	1 (0.4)	0
Musculoskeletal pain	0	0	1 (0.4)	0
Pain in jaw	0	0	2 (0.8)	0
Gastrointestinal disorders	3 (1.1)	0	4 (1.5)	0
Constipation	2 (0.8)	0	1 (0.4)	0
Diarrhoea	1 (0.4)	0	1 (0.4)	0
Colitis	0	0	1 (0.4)	0
Nausea	0	0	1 (0.4)	0
Infections and infestations	2 (0.8)	0	2 (0.8)	0

Primary system organ class Preferred term	GP2411 (N=263)		EU-Prolia (N=264)	
	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)
Conjunctivitis	1 (0.4)	0	1 (0.4)	0
Cystitis	1 (0.4)	0	0	0
Pulpitis dental	1 (0.4)	0	0	0
Urinary tract infection	1 (0.4)	0	0	0
Periodontitis	0	0	1 (0.4)	0
Skin and subcutaneous tissue disorders	2 (0.8)	0	2 (0.8)	0
Alopecia	1 (0.4)	0	0	0
Rash	1 (0.4)	0	1 (0.4)	0
Pruritus	0	0	1 (0.4)	0
Investigations	1 (0.4)	0	1 (0.4)	0
Neutrophil count decreased	1 (0.4)	0	0	0
Blood parathyroid hormone increased	0	0	1 (0.4)	0
Nervous system disorders	1 (0.4)	0	2 (0.8)	0
Headache	1 (0.4)	0	2 (0.8)	0
Vascular disorders	1 (0.4)	0	0	0
Hot flush	1 (0.4)	0	0	0
Blood and lymphatic system disorders	0	0	1 (0.4)	0
Thrombocytosis	0	0	1 (0.4)	0
Renal and urinary disorders	0	0	1 (0.4)	0
Pollakiuria	0	0	1 (0.4)	0

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.0, CTCAE version 5.0.
Source: Table 14.3.1-3.2.1

The most frequent AE with a suspected causal relationship was hypocalcaemia in both treatment groups (GP2411: 21 subjects, 8.0%; EU-Prolia: 24 subjects, 9.1%) followed by injection site reactions (GP2411: 7 subjects, 2.7%; EU-Prolia: 10 subjects, 3.8%).

Treatment period 2 (Weeks 52 to 78)

The overall incidence of aEs was similar between the continued EU-Prolia group (EU-Prolia/EU-Prolia) and the group that switched from EU-Prolia to GP2411 (EU-Prolia/GP2411) and lower in the GP2411/GP2411 group during TP2, for all grades. The overall incidence of grade 3 or 4 aEs was similar across treatment groups.

The most frequent aEs (PTs) across all treatment groups were COVID-19 infection, nasopharyngitis, and arthralgia. Hypocalcaemia was reported in 1 subject in the GP2411/GP2411 group, with grade 2.

Table 59. Study 301–- aEs, regardless of study drug relationship, by primary SOC and PT (in at least 3% of subjects in any treatment group), TP2 (TP2 SAF)

	GP2411/GP2411 N=253		EU-Prolia/EU-Prolia N=125		EU-Prolia/GP2411 N=124	
Primary system organ class Preferred term	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)
Number of subjects with at least one TEAE	68 (26.9)	5 (2.0)	47 (37.6)	2 (1.6)	48 (38.7)	2 (1.6)
Infections and infestations	22 (8.7)	1 (0.4)	27 (21.6)	1 (0.8)	17 (13.7)	1 (0.8)
COVID-19	6 (2.4)	1 (0.4)	7 (5.6)	0	2 (1.6)	1 (0.8)
Nasopharyngitis	5 (2.0)	0	4 (3.2)	0	6 (4.8)	0
Musculoskeletal and connective tissue disorders	21 (8.3)	0	14 (11.2)	1 (0.8)	10 (8.1)	0
Arthralgia	7 (2.8)	0	5 (4.0)	0	2 (1.6)	0
Injury, poisoning and procedural complications	10 (4.0)	1 (0.4)	3 (2.4)	0	11 (8.9)	1 (0.8)
Spinal compression fracture	2 (0.8)	0	2 (1.6)	0	4 (3.2)	0
Contusion	1 (0.4)	0	1 (0.8)	0	4 (3.2)	0
Metabolism and nutrition disorders	8 (3.2)	0	4 (3.2)	0	6 (4.8)	0
Gastrointestinal disorders	5 (2.0)	1 (0.4)	9 (7.2)	0	0	0
Diarrhoea	1 (0.4)	0	4 (3.2)	0	0	0
Nervous system disorders	3 (1.2)	0	3 (2.4)	0	5 (4.0)	1 (0.8)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.0, CTCAE version 5.0
Source: 5.3.5.1-301-Table 12-4

The overall incidence of aEs with a suspected causal relationship to study drug was low (GP2411/GP2411: 2.8%, EU-Prolia/EU-Prolia: 5.6%, and EU- Prolia/GP2411: 4.0%) during TP2. All were of grade 1 or 2 severity ([5.3.5.1-301-Table 12-6]).

TP1 and TP2 combined

The incidence of TEAEs for the entire study (number and percentage of subjects with aEs) was lower in the GP2411/GP2411 group compared to the Prolia/Prolia and Prolia/GP2411 groups, which showed similar percentages of patients experiencing TEAEs (63.6% vs 76.0% vs 76.6%). This imbalance in the overall incidence was mainly driven by an imbalance in the SOC 'Infections and infestations' (29.2% vs 40.0% vs 36.3%). The higher percentage in the Prolia/Prolia group was mainly driven by higher incidences of COVID-19 infection, cystitis, urinary tract infection, upper respiratory tract infection and bronchitis. The second most frequently affected SOC was''Musculoskeletal and connective tissue disorders' with comparative incidences across the three treatment groups (22.1% in GP2411/GP2411 vs 24.8% in Prolia/Prolia vs 21.8% in Prolia/GP2411). All except one TEAE in each group (back pain in GP2411/GP2411 and Prolia/GP2411 and intervertebral disc disorder in Prolia/Prolia) were of grade 1 or 2. Arthralgia, back pain and spinal osteoarthritis were the most frequently reported PTs in this SOC across the three treatment groups and also with comparable incidences across them. The third most affected SOC was 'Metabolism and nutrition disorders' (17.8% in GP2411/GP2411 vs 17.6% in Prolia/Prolia vs 21% in Prolia/GP2411). All TEAEs in this SOC were of grade 1 or 2 severity. The most common TEAE was hypocalcaemia with similar incidences across the three treatment groups (10.7% in GP2411/GP2411 vs 11.2% in Prolia/Prolia vs 9.7% in Prolia/GP2411). All the hypocalcaemia events were of grade 1 or 2 severity.

Among the treatment related TEAEs in the entire study, the overall incidence was comparable across the three groups (15% in GP2411/GP2411 vs 21.6% in Prolia/Prolia vs 20.2% in Prolia/GP2411). None of the treatment related TEAEs were of grade 3 or 4 in any of the three treatment groups. The numerically higher incidence in the Prolia/Prolia group was mainly driven by higher incidences of TEAEs in 'Metabolism and nutrition disorders' (7.9% vs 12% vs 8.1%), 'Musculoskeletal and connective tissue disorders' (2.8% vs 4.8% vs 0.8%) and 'Infections and infestations' (0.8% vs 2.4% vs 1.6%). Since none of the events leading to those numerical imbalances were of grade 3 or 4 and since the differences were only small, the imbalances are not considered clinically meaningful.

Over the entire study, the majority of TEAEs were of grade 1 or 2 in all treatment groups. Grade 3 TEAEs occurred with low and similar incidences across all treatment groups (4.3% in GP2411/GP2411, 4.8% in Prolia/Prolia, 3.2% in Prolia/GP2411). None of the grade 3 events were considered related to treatment. The SOC with most grade 3 TEAEs was 'Infections and infestations', with similar incidences across treatment groups (0.8% vs 1.6% vs 1.6%). The majority of grade 3 TEAEs occurred in single subjects.

In the TP2 SAF, grade 4 TEAEs occurred only in the GP2411/GP2411 group, but with a low incidence (3/253, 1.2%). None of these events were considered related to treatment. The events in the GP2411/GP2411 group were hip fracture, femoral neck fracture and pulmonary embolism. Considering also subjects who did not receive study drug in TP2, 1 additional subject in the Prolia group experienced TEAEs of grade 4 (metastatic neoplasm and ovarian cancer) in TP1; the subject discontinued the study before TP2.

2.6.8.3. Serious adverse event/deaths/other significant events

No deaths occurred in Study 101 in healthy male subjects.

In Study 301 in female subjects with PMO, one subject in the GP2411 treatment group died on study day 175 during TP1 (PT: sudden death). She had received one dose of GP2411 on study day 1. She died during sleep. The death was not considered to be related to study drug by the investigator. The exact cause of the death was unknown, and no autopsy was performed. This subject had a medical history of several underlying cardiovascular conditions, including hypertension, widening of the ascending aorta, impaired left ventricular relaxation, tricuspid valve incompetence, supraventricular extrasystoles, and an atrioventricular block. She was on concomitant medications including acetylsalicylic acid, atorvastatin calcium, metoprolol tartrate and trimetazidine hydrochloride. The ECG examinations of this subject performed at Screening and Visits 2 (Day 1) and 5 (Day 8) were assessed as abnormal but assessed by the investigator as not clinically significant. Laboratory evaluations for haematology, clinical chemistry, and coagulation at all visits were normal, including at Visit 10 (Day 155), 20 days before death.

The overall incidence of SAEs was "low and similar across treatment groups in Study 101 (GP2411: 3 subjects, 1.8%; EU-Xgeva: 3 subjects, 1.8%; US-Xgeva: 1 subject, 0.6%).

The following SAEs occurred:

- GP2411: Cerebral haemorrhage, Inguinal hernia, Pulmonary contusion
- EU-Xgeva: Alcohol abuse, Appendicitis, Mantle cell lymphoma
- US-Xgeva: Intervertebral disc protrusion

None of the SAEs was suspected to be related to the study drug by the investigator.

The overall incidence of SAEs was similar between both treatment groups in TP1 of Study 301. By PT, hip fracture occurred in 2 subjects in the GP2411 group; both events were not suspected to be related to the study drug by the investigator. Further results on fractures are provided below.

All other SAEs occurred only in single subjects in either treatment group. There were no SAEs with a suspected causal relationship to study drug during TP1.

Table 60. Study 301–- SAEs by primary SOC and PT, TP1 (TP1 SAF)

	GP2411 N=263		EU-Prolia N=264	
Primary system organ class Preferred term	**All Grades n (%)**	**Grades 3/4 n (%)**	**All Grades n (%)**	**Grades 3/4 n (%)**
Number of subjects with at least one serious TEAE	12 (4.6)	9 (3.4)	8 (3.0)	5 (1.9)
Injury, poisoning and procedural complications	4 (1.5)	3 (1.1)	0	0
Hip fracture	2 (0.8)	2 (0.8)	0	0
Ankle fracture	1 (0.4)	0	0	0
Femoral neck fracture	1 (0.4)	1 (0.4)	0	0
Gastrointestinal disorders	2 (0.8)	2 (0.8)	0	0
Chronic gastritis	1 (0.4)	1 (0.4)	0	0
Gastritis erosive	1 (0.4)	1 (0.4)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.8)	2 (0.8)	2 (0.8)	2 (0.8)
Breast cancer	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Malignant neoplasm of ampulla of Vater	1 (0.4)	1 (0.4)	0	0
Metastatic neoplasm	0	0	1 (0.4)	1 (0.4)
Ovarian cancer	0	0	1 (0.4)	1 (0.4)
General disorders and administration site conditions	1 (0.4)	0	0	0
Sudden death	1 (0.4)*	0	0	0
Infections and infestations	1 (0.4)	1 (0.4)	2 (0.8)	2 (0.8)
COVID-19	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Pneumonia	0	0	1 (0.4)	1 (0.4)
Nervous system disorders	1 (0.4)	0	0	0
Syncope	1 (0.4)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.4)	1 (0.4)	0	0
Pulmonary embolism	1 (0.4)	1 (0.4)	0	0
Eye disorders	0	0	1 (0.4)	0
Epiretinal membrane	0	0	1 (0.4)	0
Hepatobiliary disorders	0	0	1 (0.4)	1 (0.4)
Cholecystitis	0	0	1 (0.4)	1 (0.4)
Musculoskeletal and connective tissue disorders	0	0	1 (0.4)	0
Osteoarthritis	0	0	1 (0.4)	0
Vascular disorders	0	0	1 (0.4)	0
Thrombophlebitis	0	0	1 (0.4)	0

*death= grade 5 outcome
Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.0, CTCAE version 5.0.
Source: 5.3.5.1-301-Table 12-9

The incidence and nature of SAEs was similarly low across all treatment groups in TP2. There were no SAEs with a suspected causal relationship to study drug during TP2.

Table 61. Serious adverse events by primary system organ class and preferred term, TP2 (TP2 SAF)

	GP2411/GP2411 N=253		EU-Prolia/EU-Prolia N=125		EU-Prolia/GP2411 N=124	
Primary system organ class Preferred term	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)
Number of subjects with at least one serious TEAE	4 (1.6)	3 (1.2)	2 (1.6)	1 (0.8)	0	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2 (0.8)	2 (0.8)	0	0	0	0
Colon cancer	1 (0.4)	1 (0.4)	0	0	0	0
Malignant neoplasm of ampulla of Vater	1 (0.4)	1 (0.4)	0	0	0	0
Gastrointestinal disorders	1 (0.4)	1 (0.4)	1 (0.8)	0	0	0
Intestinal ischaemia	1 (0.4)	1 (0.4)	0	0	0	0
Pancreatic fistula	1 (0.4)	1 (0.4)	0	0	0	0
Gastrointestinal inflammation	0	0	1 (0.8)	0	0	0
Injury, poisoning and procedural complication	1 (0.4)	1 (0.4)	0	0	0	0
Hip fracture	1 (0.4)	1 (0.4)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.4)	0	0	0	0	0
Pneumothorax spontaneous	1 (0.4)	0	0	0	0	0
Infections and infestations	0	0	2 (1.6)	1 (0.8)	0	0
Gastroenteritis clostridial	0	0	1 (0.8)	1 (0.8)	0	0
Gastrointestinal candidiasis	0	0	1 (0.8)	0	0	0
Musculoskeletal and connective tissue disorders	0	0	1 (0.8)	0	0	0
Osteoarthritis	0	0	1 (0.8)	0	0	0

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.0, CTCAE version 5.0

Injection site reactions

In both studies, the s.c. injection of study drug was administered only in the abdomen to reduce variability in the PK analysis. Thus, the abdomen was the only localization of ISR. ISRs were assessed by the investigator/designee and classified by CTCAE grading.

Overall, 3 subjects experienced ISRs during the Study 101, 1 (0.6%) subject in the GP2411 group and 2 (1.2%) subjects in the US-Xgeva group. All ISRs were grade 1. None of the ISRs were reported as serious or led to discontinuation of study participation. There were no clinically meaningful differences between the treatment groups in terms of VAS scores.

In Study 301, the proportion of subjects reporting ISRs was similar between the two treatment groups during TP1. All ISRs were grades 1 or 2 in severity.

During TP2, one grade 1 ISR occurred in one subject in the GP2411/GP2411 group. There were no ISRs in the EU-Prolia/EU-Prolia and EU- Prolia/GP2411 groups in TP2.

Table 62. Study 301–- ISRs during TP1 (TP1 SAF)

Maximum grade	GP2411 N=263 n (%)	EU-Prolia N=264 n (%)
Number of subjects with at least one treatment-emergent ISR	7 (2.7)	10 (3.8)
Grade 1	6 (2.3)	9 (3.4)
Grade 2	1 (0.4)	1 (0.4)
Grade 3	0	0
Grade 4	0	0
Serious treatment-emergent ISRs	0	0
Treatment-emergent ISRs leading to study or study drug discontinuation	0	0

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.0, CTCAE version 5.0.
Source: 5.3.5.1-301-Table 12-12

Hypersensitivity reactions (Study 301 only)

To analyse the potential impact of ADAs/nAbs on safety, occurrence of aEs indicative of hypersensitivity or anaphylactic reactions were assessed, with a particular focus on the potential impact of the switch from EU-Prolia to GP2411 in a subgroup of subjects in TP2. There were no aEs with the PTs "hypersensitivity" or "anaphylactic reaction" reported by the investigators during either TP1 or TP2, but screening with the SMQs "hypersensitivity" and "anaphylactic reaction" retrieved 5 aEs in TP2.

Table 63. Study 301–- aEs retrieved by SMQ screening in TP2

Treatment group AE	Days after third dosing	CTCAE grade[1]	Related to study drug[2]	ADA status at time of AE onset	Sponsor's assessment
EU-Prolia/GP2411					
Dermatitis allergic	35	2	No	Negative[3]	Dermatitis is listed in the Prolia label, i.e., it is a known adverse drug reaction of denosumab. Event not considered an ADA associated hypersensitivity reaction.
Rhinitis allergic	143	1	No	Negative[4]	Event not considered an ADA associated hypersensitivity reaction.
EU-Prolia/EU-Prolia					
Urticaria	1	2	Yes	Negative[3]	Urticaria is listed in the Prolia label, i.e., it is a known adverse drug reaction of denosumab. Event not considered an ADA associated hypersensitivity reaction.
GP2411/GP2411					
Conjunctivitis allergic	158	2	No	Negative[3]	Event not considered an ADA associated hypersensitivity reaction.
Seasonal allergy	166	2	No	Negative[3]	Event not considered an ADA associated hypersensitivity reaction.

1: CTCAE version 5.0
2: Relationship assessed by Investigator
3: ADA samples were assessed negative, both at study visit before and at study visit after onset of AE
4: ADA sample was negative at study visit before onset of AE. Duration of AE was 2 days. Subject was ADA positive (titer negative) at the next ADA assessment (end of study visit) by which time the AE had resolved.
Source: ([5.3.5.1-301-Table 14.3.1-6], [5.3.5.1-301-Listing 16.2.7-1], and [5.3.5.1-301-Listing 16.2.9-2]).

In TP2, there were no ADA associated hypersensitivity reactions in any of the treatment groups, including subjects who underwent the switch from EU-Prolia to GP2411. In conclusion, following the switch from EU-Prolia to GP2411, there was no increase in the incidence of ADAs, and there were no ADA-associated hypersensitivity reactions in the EU-Prolia/GP2411 group.

Vertebral fractures (Study 301 only)

Independent radiologists at the central imaging vendor assessed lateral thoracic (vertebrae T4 to T12) and lumbar (vertebrae L1 to L4) spine radiographs for vertebral fractures using the Genant grading scale (Genant et al 1993). X-ray evaluations for vertebral fractures were performed at Screening, Week 52 (Visit 15), and Week 78 (EOS Visit). The central X-ray reading methodology was described in an Osteoporosis Independent Review Charter ([5.3.5.1- 301-Appendix 16.1.1]).

There were no clinically meaningful differences between treatment groups with regard to the incidence and severity of vertebral fractures in TP1.

Table 64. Study 301-- Vertebral fractures based on central imaging, TP1 (TP1 SAF)

	GP2411 N=263 n (%)	EU-Prolia N=264 n (%)
Number of subjects with at least one vertebral fracture at baseline	123 (46.8)	116 (43.9)
Maximum Genant Score		
1	82 (31.2)	88 (33.3)
2	41 (15.6)	28 (10.6)
3	0	0
Number of subjects with new vertebral fractures	15 (5.7)	24 (9.1)
Maximum Genant Score		
1	8 (3.0)	21 (8.0)
2	7 (2.7)	3 (1.1)
3	0	0
Number of subjects with worsening vertebral fractures*	3 (1.1)	3 (1.1)
Maximum Genant Score		
2	3 (1.1)	3 (1.1)
3	0	0

* calculated on the entire SAF as denominator.
Source: 5.3.5.1-301-Table 12-13

The incidences of new vertebral fractures were comparable across the treatment groups in TP2.

Table 65. Study 301-- Vertebral fractures based on central imaging, TP2 (TP2 SAF)

	GP2411/GP2411 N=253 n (%)	EU-Prolia/EU-Prolia N=125 n (%)	EU-Prolia/GP2411 N=124 n (%)
Number of subjects with at least one vertebral fracture at Week 52	126 (49.8)	57 (45.6)	65 (52.4)
Maximum Genant Score			
1	81 (32.0)	42 (33.6)	53 (42.7)
2	45 (17.8)	15 (12.0)	12 (9.7)
3	0	0	0
Number of subjects with new vertebral fractures	12 (4.7)	3 (2.4)	8 (6.5)
Maximum Genant Score			
1	9 (3.6)	3 (2.4)	7 (5.6)
2	3 (1.2)	0	0
3	0	0	1 (0.8)
Number of subjects with worsening vertebral fractures*	1 (0.4)	0	0
Maximum Genant Score			
2	0	0	0
3	1 (0.4)	0	0

* calculated on the entire SAF as denominator.
Source: 5.3.5.1-301-Table 12-14

Non-vertebral fractures (Study 301 only)

Non-vertebral fractures were diagnosed based on local radiology reports (no central X-ray reading required). The incidences of non-vertebral fractures were low and similar across the treatment groups in TP1 and TP2.

Table 66. Study 301 – Non-vertebral fractures reported as aEs, TP1 (TP1 SAF)

	GP2411 N=263		EU-Prolia N=264	
Category Preferred term	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)
Hip fractures	3 (1.1)	3 (1.1)	1 (0.4)	0
Hip fracture	2 (0.8)	2 (0.8)	0	0
Femoral neck fracture	1 (0.4)	1 (0.4)	0	0
Femur fracture	0	0	1 (0.4)	0
Other non-vertebral fractures	2 (0.8)	1 (0.4)	2 (0.8)	0
Ankle fracture	1 (0.4)	0	1 (0.4)	0
Wrist fracture	1 (0.4)	1 (0.4)	0	0
Radius fracture	0	0	1 (0.4)	0

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.0, CTCAE version 5.0.
Source: 5.3.5.1-301-Table 12-15

The overall incidence of non-vertebral fractures in all groups in both treatment periods was low and similar in both treatment periods (TP1: 1.9% in GP2411 vs 1.1% in Prolia; TP2: 0.8% in GP2411/GP2411 vs 0 in Prolia/Prolia vs 0.8% in Prolia/GP2411). There was a numerical difference in the incidence of SAEs and in grade 3 or 4 non-vertebral fractures between the GP2411 and Prolia groups. However, none of the SAEs was considered related to study treatment, nor did they lead to study or treatment discontinuations and the patients recovered from these events.

2.6.8.4. Laboratory findings

Study 101 in healthy male subjects

In Study 101, clinical laboratory evaluations for haematology, clinical chemistry, coagulation, and urinalysis were performed.

As expected, a decrease in serum calcium from baseline levels was observed at the Day 4 visit and consecutively the levels were maintained for the next visits. In the later part of the study (from Day 85 onwards) a trend to a nominal return towards normal serum calcium levels was observed, though the mean and median serum concentrations continued to remain below the baseline levels at the end of the study. Overall, trends in serum calcium were similar across the three treatment groups throughout the study and in line with the established nature of serum calcium profiles after denosumab administration. Clinical symptoms of hypocalcaemia were not observed in any study subject. Calcium levels over time are depicted in the section on Adverse Events.

A similar trend was observed for serum phosphate. An expected fall in serum phosphate levels was seen on Day 4 and then maintained for the rest of the study, with a trend towards return to normal levels. The overall

decline in serum phosphate levels was similar across the three treatment groups none of the observed cases were considered as clinically significant.

Trend and summary data of other clinical laboratory parameters (haematology, clinical chemistry and coagulation parameters) were overall comparable across the three treatment groups throughout the study and generally within normal range. While consistent levels were maintained for most parameters, for a few parameters like haemoglobin, haematocrit and erythrocyte count, there appears to be a small fall from baseline at Day 4 after which the values are maintained at the same level throughout the rest of the study.

The analysis demonstrates that for all clinical laboratory parameters assessed in Study 101, there were no clinically meaningful differences across the three treatment groups in the entire duration of the study. No unexpected and significant laboratory abnormalities were observed in any of the treatment groups. Hypocalcaemia and hypophosphatemia were observed around expected lines as per the established safety profile for denosumab. No grade 4 laboratory abnormalities were seen while a single transient case of grade 3 elevation occurred for AST levels in a subject. All laboratory changes observed were transient in nature with prompt reversal to normal levels.

Study 301 in female subjects with PMO

In Study 301, clinical laboratory evaluations were performed for haematology, clinical chemistry, coagulation, and urinalysis.

The mean and median serum calcium levels at baseline were comparable across the three treatment groups and remained comparable up to the end of the study. The mean and median change from baseline of serum calcium at End of Study was low and similar across the three treatment groups.

From baseline levels, there was an initial decrease in mean and median calcium levels after the first dose of study treatment, which recovered in the next visits and continued at steady calcium levels until the end of the study. There was no grade 3 or 4 hypocalcaemia. One patient in the Prolia/GP2411 group had serum calcium level of 1.9 mmol/L (grade 2) at Visit 6 which became normal (2.38 mmol/L) approximately a week later and remained normal till the end of the study. This patient did not have any symptoms suggestive of hypocalcaemia during that time. No other patient had a calcium value of <1.9 mmol/L. There was also no grade 3 or 4 hypercalcaemia. There was one patient in Prolia/Prolia group with a serum calcium of 3.04 mmol/L (grade 2) at Visit 16 which came down to normal level (2.45 mmol/L) in the next visit (End of Study visit). This patient did not have any symptoms suggestive of hypercalcemia during that time. No other patient had a calcium value of >3.0 mmol/L. Calcium levels over time are depicted in the section on Adverse Events.

The overall trend of serum phosphate through the duration of the study was similar across the three treatment groups. There was a slight decrease in mean and median phosphate level at Visit 10 (although within normal range), but the levels increased over the next visits and continued a steady phosphate level until the end of the study. No aEs of low serum phosphate level were reported. Serum phosphate levels slightly higher or lower than normal were seen in only few patients. They were considered not clinically significant by the investigators and no aEs of hypo- or hyperphosphatemia were reported.

Trend and summary data of haematology parameters throughout the study across the three treatment groups were comparable and generally within normal range. As the study was conducted in a population of post-menopausal women, some abnormalities are expected. For haemoglobin, the normal range was 120-160 g/L. Most of the patients had normal haemoglobin levels with only few patients with grade 2 (80-<100 g/L) haemoglobin levels. One patient in GP2411/GP2411 group had haemoglobin of 69 g/L (grade 3) at Visit 15

that was reported as an AE. No concomitant medications were given. The serum LDH level for this patient was normal at this time and throughout the study. Haemoglobin was retested 10 days later at an unscheduled visit and the value was 138 g/L (normal value). Subsequently, the patient's haemoglobin was 138 g/L at End of Study.

Trend and summary data of liver and kidney parameters through the study were comparable across the three treatment groups and generally within normal range. Serum electrolytes were also generally within normal range. Some abnormalities are expected in this population.

In 2 patients, isolated AST and ALT values of >6x ULN (ULN for AST 41 U/L, ULN for ALT 45 U/L) were reported. In one patient, the values returned to normal in subsequent visits and remained normal till End of Study. In the other patient, AST returned to normal and ALT value was <2x ULN at End of Study. Bilirubin values were normal in these patients and ALP was not raised >5x ULN (ULN for ALP 104 U/L). No bilirubin levels were of grade 3 or 4 in the entire study across the treatment groups. No ALP values were >5x ULN in the entire study across the treatment groups.

No patient had low serum albumin in the entire study across the treatment groups. No grade 3 AEs of increased creatinine or increased or decreased potassium levels were reported. 3 patients had single isolated cases of grade 3 hypernatremia reported (sodium level >155 – 160 mmol/L) but the values returned to normal in subsequent visits. One patient (GP2411/GP2411) had grade 3 hyponatremia (sodium level 120 – 124 mmol/L) at screening and baseline, but subsequently the sodium level increased during the study and was 132 mmol/L at End of Study. No symptoms of hyponatremia were reported as AE for this patient.

Also, trend and summary data of coagulation parameters through the study were comparable across the three treatment groups and generally within normal range. No effect of denosumab is expected on the coagulation parameters as per Prolia SmPC (2023).

In conclusion for clinical laboratory parameters, there were no clinically meaningful differences across the three treatment groups in the entire duration of the study.

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

ADA assay validation

The Applicant has adopted an electrochemiluminescence (ECL) bridging immunoassay to screen, confirm and quantify denosumab specific antibodies in human serum of healthy volunteers and patients with post-menopausal osteoporosis. In brief, serum samples are acidified and neutralised before interacting with both biotin-labelled and sulfo-tag labelled denosumab. ECL measurement is performed on a Meso Scale Discovery (MSD) Sector Imager reader in duplicates. The negative control consisted of a commercially available human serum pool (male healthy volunteers) and 17 (individual PMO patient) sera which were further spiked with a polyclonal rabbit immune response (anti-denosumab F(a'')2-fragment) to serve as positive control. Final

concentration levels in 100% serum were 20, 100, 500, 5000 and 20000 ng/mL. All critical reagents, drugs, matrices and antibodies and used lot numbers were well described. The assay was validated with respect to cut-points (screening, confirmatory), precision, specificity, selectivity, target- and drug-interference, and the analyte was tested for stability (short-term, freeze/thaw).

A floating screening cut point has been estimated in 50 individual human serum samples from healthy volunteers and 51 PMO samples and is defined as Blank x NF (1.11 HV; 1.09 PMO) with a 5% false positive rate. The confirmatory cut point (1% false positive rate) is set at 26.7% (HV) and 28.8% (PMO) signal reduction. Cut points for titer assay were defined as Blank x NF (1.42 HV; 1.36 PMO). Minimal required dilution was determined to be 1:2. Screening assay sensitivities (limit of detection) were 4.0 ng/mL and 9.0 ng/mL in 100% human serum pool of HV and PMO, respectively with 95% consistency. Intra- and inter-run precision were both ≤ 15% CV (Screening assay). Selectivity analyses included lipemic and hemolytic serum samples, showing no matrix-related interference. Freeze-thaw sample stability (demonstrated for 8 cycles at a nominal -70°C) as well as short-term storage stability of anti-denosumab antibodies in human serum was demonstrated for 7 days at 2-8°C and for up to 72 hours at room temperature. No long-term stability validation experiments were performed but provided literature reference is considered adequate. Specificity of the assay for anti-denosumab antibodies could be demonstrated using GP2411.01REF, GP2411-LIVI, GP2411-LISY, Xgeva, or Prolia. The assay was tested to detect positive samples in the presence of the drug and was shown to be tolerant to concentrations of at least 30 µg/mL in both HV and PMO serum at ADA concentrations as low as 500 ng/mL. The absence of a prozone effect was confirmed for anti-denosumab IgG levels up to 40,000 ng/mL.

Taken together, the adopted three-tiered approach for determination of ADAs was well described and developed. It is considered state of the art and valid for its intended use.

nAb assay validation

The Applicant presented an electrochemiluminescence (ECL) assay for the detection of neutralising ADA's in human serum (healthy volunteers; post-menopausal osteoporosis patients). In brief, free anti-denosumab antibodies were incubated on a GP2411 coated plate after acid dissociation and washed. After a second acid dissociation step free anti-denosumab antibodies were incubated with sulfo-tag labelled GP2411 and the solution was transferred to a NFκB ligand (RANKL) coated plate. The presence of neutralizing antibodies against denosumab would inhibit the interaction of GP2411-Sulfo with RANKL, which is reflected by assay signal reduction. The negative control consisted of a commercially available human serum pool (male healthy volunteers) and 26 (individual PMO patient) sera which were further spiked with a human anti-denosumab IgG1 antibody to serve as positive control. Final concentration levels in 100% serum were 150, 250, 500 and 1000 ng/mL. All critical reagents, drugs, matrices and antibodies and used lot numbers were well described. The nAb assay was validated with respect to cut-point, precision, selectivity, target- and drug-interference, and the analyte was tested for stability (short-term, freeze/thaw).

A fixed cut-point (10% neutralization) was calculated from 50 individual serum samples of healthy volunteers and 50 individual serum samples of patients with PMO after 1:2 dilution. The assay sensitivity was determined to be 155 ng/mL in 100% human serum pool from HV and 123 ng/mL in 100% human serum pool from patients with PMO for 95% consistency. Assay sensitivities (limit of detection) were 155 ng/mL and 123 ng/mL in 100% human serum pool of HV and PMO, respectively. Intra- and inter-run precision were both ≤ 12% CV. No prozone effect was observed. 10 individual human serum samples from HV and 10 individual human serum samples from patients with PMO spiked with positive control (150 ng/mL and 5000 ng/mL) were used for selectivity analyses and included lipemic and hemolytic samples. No matrix-related interferences were observed. The assay was tested to detect positive samples in the presence of the drug

(neutralizing anti-denosumab antibody concentrations: 1,000 ng/mL, 250 ng/mL and 150 ng/mL) and was shown to be tolerant to concentrations of 20 µg/mL in 100% human serum. Freeze-thaw sample stability (demonstrated for 8 cycles at a nominal -70°C) as well as short-term storage stability of anti-denosumab antibodies in human serum was demonstrated for 7 days at 2-8°C and for up to 72 hours at room temperature. No long-term stability validation experiments were performed but provided literature reference is considered adequate. The maximal concentration of target (RANKL), which led to a signal below the cut-point was 500 pg/mL in 100 % serum.

Taken together, presented assay for determination of neutralising properties was well described and established. It was setup correctly and validated.

In both clinical studies, immunogenicity was assessed by measuring ADAs, including titers and neutralizing capacity, in the serum of all subjects. Both studies compared the immunogenicity of GP2411 with Xgeva/Prolia.

Study 101

On Day 1, subjects received a single s.c. dose of 35 mg GP2411, EU-Xgeva or US-Xgeva. Thereafter, the subjects returned to the site for 14 scheduled ambulatory visits for PK, PD, ADA and safety assessments over a period of 39 weeks. Thirteen ADA samples/subject were collected over a period of 39 weeks (9 months) after the single dose of 35 mg denosumab; the sampling schedule was aligned with the PK sampling from Day 11 on.

Pre-exposure samples were taken to evaluate the potential for pre-existing antibodies. The early post-exposure timepoints from Week 2 to Week 8 were appropriate to observe a potential early immune response, including IgM and IgG formation. After this initial period, samples were collected every 4 weeks up to Week 39 to ensure close monitoring of potential ADA development that also enables the evaluation of transient ADAs.

Similar proportions of subjects across all treatment groups tested positive for ADAs and nAbs, respectively (see table below). The proportions of subjects with at least one positive ADA response or with nAbs at individual visits were also similar across treatment groups.

The number of subjects with nAbs or with persistent ADAs was low. None of the nAb-responses were persistent.

The incidence of ADAs reported in this study was higher in all 3 treatment groups than the overall incidence of <1% reported from historical studies with Xgeva in the Xgeva SmPC and Xgeva USPI. For interpreting this higher incidence, the high sensitivity of the ADA assay used in this study (6 ng/mL) needs to be considered. Furthermore, all measured samples were 'ADA titer negative', which means that the concentration was below the cut-point for the titer assay (<20 ng/mL) and titers were therefore not quantifiable in any sample.

Table 67. Study 101–- ADA status overall (SAF)

Visit	Category	GP2411 N=166 n (%)	EU-Xgeva N=171 n (%)	US-Xgeva N=162 n (%)
Overall	ADA positive	96 (57.8)	111 (64.9)	112 (69.1)
	ADA titer negative	96 (57.8)	111 (64.9)	112 (69.1)
	NAb positive	2 (1.2)	1 (0.6)	0
	NAb negative	94 (56.6)	110 (64.3)	112 (69.1)
	Transient	95 (57.2)	110 (64.3)	111 (68.5)
	Persistent	1 (0.6)	1 (0.6)	1 (0.6)
	ADA negative	70 (42.2)	60 (35.1)	50 (30.9)
Positive ADA/NAb tests by visit				
Baseline (before single dose)	ADA positive	1 (0.6)	0	0
Visit 6	ADA positive	2 (1.2)	5 (2.9)	3 (1.9)
Visit 7	ADA positive	1 (0.6)	5 (2.9)	6 (3.7)
Visit 8	ADA positive	5 (3.0)	7 (4.1)	8 (4.9)
Visit 9	ADA positive	9 (5.4)	22 (12.9)	22 (13.6)
Visit 10	ADA positive	29 (17.5)	42 (24.6)	49 (30.2)
Visit 11	ADA positive	64 (38.6)	62 (36.3)	69 (42.6)
Visit 12	ADA positive	32 (19.3)	36 (21.1)	44 (27.2)
	NAb positive	1 (0.6)	1 (0.6)	0
Visit 13	ADA positive	10 (6.0)	6 (3.5)	10 (6.2)
Visit 14	ADA positive	2 (1.2)	0	2 (1.2)
Visit 15	ADA positive	2 (1.2)	0	0
Visit 16	ADA positive	1 (0.6)	1 (0.6)	0
	NAb positive	1 (0.6)	0	0
End of Study	ADA positive	2 (1.2)	1 (0.6)	2 (1.2)
	NAb positive	1 (0.6)	0	0

For individual visits, NAb and titer status are only shown when positive.
'Transient' indicates a patient with a positive ADA result but not qualifying as 'Persistent'.
'Persistent' indicates a subject with a positive ADA result at the final visit and with at least 2 consecutive positive ADA results, irrespective of missing results.
'ADA titer negative' indicates an ADA level ranging from 6 - 20 ng/mL.
Source: [5.3.3.1-101-Table 14.3-4]

Impact of ADA/nAb on safety (Study 101)

No adverse events that could possibly be linked to immunogenicity (e.g. anaphylactic or hypersensitivity reactions) were reported overall in the study, including in ADA positive subjects.

Study 301

In TP1 (Day 1 to Week 52), subjects received 2 doses of 60 mg study medication (GP2411 or EU-Prolia) s.c., one dose on Day 1 and one at Week 26.

At Week 52 (start of TP2), 50% of subjects treated with EU-Prolia in TP1 switched to treatment with GP2411 while the other 50% continued treatment with EU-Prolia. All subjects treated with GP2411 in TP1 continued treatment with GP2411 in TP2 (blinded re-randomization. Subjects received 1 dose of 60 mg study medication (GP2411 or EU-Prolia) s.c., at Week 52. Twelve ADA samples per subject were collected, i.e. at

Day 1 (pre-dose), then Weeks 2, 8, 14, 18, 22, 26 (pre-dose), 39, 52 (pre-dose), 56, 65, and 78. ADA sampling was aligned with the PK sampling from Week 2 onwards.

Pre-exposure samples were taken to evaluate the potential for pre-existing antibodies. Sampling was more frequent in the period between the first (Day 1) and second (Week 26) dose and then less frequent up to Week 78. The early post-exposure timepoints in Weeks 2 and 8 were appropriate to observe a potential early immune response, including IgM and IgG formation. After this initial period, samples were collected every 4 weeks up to Week 26 (second dose). From Week 26 onwards, samples were taken on a regular basis up to end of study at Week 78.

The incidences of ADAs and NAbs "were similar" in both treatment groups at all time points during TP1. Overall, 35.4% of subjects were ADA positive in the GP2411 compared to 40.9% in the EU-Prolia group.

Of note, the ADA positive subjects, except for 4 (2 subjects, 0.8%, in each treatment group), had a negative titer result which indicates an extremely low immune response to denosumab that could only be detected with the highly sensitive ADA assay used in this study.

Also in TP2, no differences were detected between GP2411 and EU-Prolia in terms of immunogenicity. The incidences of ADAs were similar between subjects who switched from EU-Prolia to GP2411 compared with those who continued on EU-Prolia: EU-Prolia/GP2411: 26/124 subjects, 21.0%; EU-Prolia/EU-Prolia: 26/125 subjects, 20.8%.

There was no increase in ADA titers, persistent ADA responses or incidence of NAbs after switching from EU-Prolia to GP2411.

Table 68. ADA status during TP2 (TP1+TP2, TP2 SAF)

Visit	Category	GP2411/ GP2411 N=253 n (%)	EU-Prolia/ EU-Prolia N=125 n (%)	EU-Prolia/ GP2411 N=124 n (%)
Overall TP2	ADA Positive	42 (16.6)	26 (20.8)	26 (21.0)
	ADA titer positive	0	1 (0.8)	0
	NAb Positive	1 (0.4)	0	1 (0.8)
	Transient	39 (15.4)	23 (18.4)	26 (21.0)
	Persistent	3 (1.2)	3 (2.4)	0
Overall TP1+TP2	ADA Positive	113 (44.7)	58 (46.4)	60 (48.4)
	ADA titer positive	2 (0.8)	2 (1.6)	0
	NAb Positive	2 (0.8)	1 (0.8)	1 (0.8)
	Transient	108 (42.7)	53 (42.4)	57 (46.0)
	Persistent	5 (2.0)	5 (4.0)	3 (2.4)
Positive ADA/NAb tests and ADA titer by visit				
Visit 15 (before third dose)	ADA Positive	33 (13.0)	14 (11.2)	19 (15.3)
	ADA titer positive	1 (0.4)	1 (0.8)	0
	NAb Positive	1 (0.4)	1 (0.8)	0
Visit 16 (Week 56)	ADA Positive	4 (1.6)	3 (2.4)	2 (1.6)
	ADA titer positive	0	0	0
	NAb Positive	1 (0.4)	0	0
Visit 17 (Week 65)	ADA Positive	10 (4.0)	8 (6.4)	2 (1.6)
	ADA titer positive	0	1 (0.8)	0
	NAb Positive	1 (0.4)	0	0
End of study (Week 78)	ADA Positive	32 (12.6)	18 (14.4)	22 (17.7)
	ADA titer positive	0	1 (0.8)	0
	NAb Positive	1 (0.4)	0	1 (0.8)

For individual visits, NAb and titer status are only shown when positive.
'Transient' indicates a patient with a positive ADA result but not qualifying as 'Persistent'.
'Persistent' indicates a subject with a positive ADA result at the final visit and with at least 2 consecutive positive ADA results, irrespective of missing results.
Subjects with no ADA samples at a visit are not included in the subject count for the respective visit.
'ADA titer negative' indicates an ADA level ranging from 9 - 20 ng/mL.
Source: [5.3.5.1-301-Table 14.3-5.4]

Impact of ADa/NAb on clinical safety (Study 301)

The safety profiles of GP2411 and EU-Prolia were similar in both treatment periods of Study 301.

To analyse the potential impact of ADAs/NAbs on safety, occurrence of AEs indicative of hypersensitivity or anaphylactic reactions were assessed, with a particular focus on the potential impact of the switch from EU-Prolia to GP2411 in a subgroup of subjects in TP2.

There were no ADA associated hypersensitivity reactions in any of the treatment groups, including subjects who underwent the switch from EU-Prolia to GP2411. In conclusion, following the switch from EU-Prolia to GP2411, there was no increase in the incidence of ADAs and there were no ADA-associated hypersensitivity reactions in the EU-Prolia/GP2411 group.

In conclusion, the incidence of ADAs is similar among all studies and treatment groups including switching from Prolia to the proposed biosimilar product, GP2411. All samples which tested positive for ADAs had very

low titers, and the vast majority of ADAs was non-neutralizing. The detected ADAs or NAbs did not impact PK, PD, efficacy or safety parameters. Therefore, any observed immunogenicity of GP2411 as well as Xgeva/Prolia was concluded as not clinically meaningful, and there were no differences in the immunogenicity profile of GP2411 compared to Xgeva/Prolia.

The increased ADA incidence compared to published data (i.e. ADA incidence <1%) is explained based on two factors: (1) the highly sensitive assays and (2) the frequent sampling scheme. The observed incidence of ADAs is highly dependent on the sensitivity and specificity of the assay. Therefore, immunogenicity data from Studies 101 and 301 cannot be compared to historical studies as different assays were used.

Taking all points together, the thorough immunogenicity assessment of GP2411 demonstrated that there were no clinically meaningful differences between Jubbonti and Xgeva/Prolia in terms of immunogenicity. Further, the risk in terms of safety or diminished efficacy of alternating or switching between use of GP2411 and the reference product Prolia is not greater than the risk of using Prolia without such alternation or switch.

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 Study 101, one subject experienced an AE leading to discontinuation of study participation; the subject was in the GP2411 group. The event was cerebral haemorrhage. It was also reported as an SAE and was not suspected to be related to the study medication by the investigator.

In Study 301, the overall incidence of AEs leading to study discontinuation was similar across all treatment groups. All of the events occurred during TP1 and none of these AEs had a suspected causal relationship to study drug. One subject in the EU-Prolia group permanently discontinued study drug during TP1 because of appendicitis. The case was reported as a non-serious AE with a severity grade 3 (no hospitalization, not considered life-threatening; the subject was treated conservatively with oral antibiotics and anti-emetic drug). A causal relationship to study drug was not suspected. This subject prematurely discontinued the study approximately 2.5 months after recovery from this AE (on study day 416); the recorded reason for study discontinuation was subject decision.

In conclusion, the overall incidence of AEs leading to study discontinuation was low across all treatment groups in both studies; none of these AEs was considered related to study drug.

2.6.8.10. Post marketing experience

Not available.

2.6.9. Discussion on clinical safety

The safety of GP2411 was evaluated in a PK and PD study in healthy adult male subjects (Study 101) and in an integrated PK, PD, confirmatory efficacy, safety, and immunogenicity study in female subjects with PMO (Study 301). The comparator drugs in Study 101 were EU-Xgeva and US-Xgeva. The comparator drug in Study 301 was EU-Prolia.

In accordance with the Prolia and Xgeva label recommendations, adequate measures were taken for the correction of pre-existing hypocalcemia by adequate intake of calcium and vitamin D before initiating denosumab therapy, as well as clinical monitoring of calcium levels before each dose and throughout treatment in both studies.

In Study 101, safety assessments after the single dose of 35 mg s.c. study drug consisted of AEs and SAEs, local tolerance (ISRs and subject-provided VAS score), physical examination, vital signs (blood pressure, pulse rate, and body temperature), ECG, and clinical laboratory tests (hematology, chemistry, coagulation and urinalysis). Furthermore, ADA formation against GP2411, EU-Xgeva, and US-Xgeva was also evaluated.

In Study 301, safety assessments after dosing consisted of AEs and SAEs, ISRs, physical examination, vital signs (blood pressure, pulse rate, and body temperature), ECG, and clinical laboratory tests (hematology, chemistry, calcium, coagulation and urinalysis). In addition, X-ray images for vertebral fractures were analyzed by a central imaging vendor. The randomization and first administration of study drug were performed based on the results of safety assessments from the Screening Period. However, imbalances are noted in the distribution of medical history between groups (see below).

Study 301 consisted of 2 treatment periods: Treatment Period 1 (TP1) from Day 1 to Week 52 and TP2 from Weeks 52 to 78. Safety data are presented by TP1 and TP2. Subjects initially received two 60 mg s.c. injections by PFS of GP2411 or EU-Prolia at 26-week intervals during TP1. At Week 52, all subjects in the GP2411 group continued treatment with a third dose of GP2411. Subjects who had received EU-Prolia during TP1 were re-randomized in a 1:1 ratio to either continue treatment with a third dose of EU-Prolia or switch to GP2411 during TP2.

Both studies took place during the COVID-19 pandemic. In Study 101, subjects with a positive result for a SARS-CoV-2 test performed on site at the day before randomization were excluded. An RT-PCR test was used for this screening test. In Study 301, local standards at the different study centers were followed for the identification of COVID-19 positive subjects who were then excluded from the study.

The SAF of Study 101 included all subjects who received at least one dose of study treatment. Subjects were analyzed according to the study treatment received. In total, the SAF consisted of 499 healthy male subjects. Of those, 166 subjects received one dose of 35 mg GP2411.

In Study 301, two separate SAF were assessed for treatment periods 1 and 2. The TP1 SAF consisted of all 527 randomized subjects treated in TP1. The TP2 SAF consisted of 502 subjects treated in TP2. Overall, 387 female PMO patients received GP2411 in Study 301; of those, 263 patients received only GP2411 (8 received one dose, 2 received two doses and 253 received three doses); additionally, 124 patients received one dose of GP2411 in TP2 following 2 doses of Prolia in TP1.

Overall, the design of the clinical studies is considered adequate for a comprehensive safety and immunogenicity assessment of GP2411. The safety assessments performed during Studies 101 and 301 were designed to capture the known safety issues listed in the Prolia and Xgeva labels and are considered appropriate. The available safety data and extent of exposure is considered adequate to assess the safety of GP2411 vs. Amgen’s denosumab.

Demographics and baseline characteristics were overall balanced between the treatment groups in both studies.

With regard to relevant medical histories and current medical conditions, an imbalance is noted in the percentage of subjects between groups in the TP1 SAF set with the following medical histories, all of which were more frequent in the Prolia group: musculoskeletal and connective tissue disorders (47.5% for GP2411

and 57.6% for Prolia); gastrointestinal disorders (21.7% and 33.0%); psychiatric disorders (8.0% and 13.3%); ear and labyrinth disorders (3.4% and 6.8%). However, adverse events observed in these categories were well balanced between treatment groups and the observed imbalances at baseline are not considered to have a major impact on the bio-similarity assessment.

In Study 101, more than 70% of subjects experienced at least one AE, most of which were of grade 1 or 2. Grade 3 or 4 AEs occurred in less than 2% of subjects and no deaths were recorded in this study.

The overall incidence of SAEs was low and similar across treatment groups (1.8%, 1.8% and 0.6% for GP2411, EU-Xgeva and US-Xgeva, respectively). None of the SAEs was considered treatment related by the investigator.

The overall percentage of subjects with AE was similar across treatment groups (72.9%, 76.0% and 71.0% for GP2411, EU-Xgeva and US-Xgeva, respectively). Also on SOC level, similar incidences were observed between the GP2411 group and the EU-Xgeva group.

Imbalances of >5% between the GP2411 group and the US-Xgeva group were observed for the SOCs Infections and infestations, Nervous system disorders, Respiratory, thoracic and mediastinal disorders, and General disorders and administration site conditions. For these SOCs, the incidences were generally higher in the GP2411 group compared to the US-Xgeva group. However, they were not considered clinically meaningful as they were driven by a few AEs reported by a low number of subjects.

The most frequent AEs on PT level were headache, COVID-19 and hypocalcaemia.

A total of 7 subjects experienced AEs of grade 3 and they were evenly distributed across groups. None of the grade 3 AEs were considered related to study treatment by the investigator.

Hypocalcaemia, a known adverse reaction for Xgeva, was documented as AE when calcium levels were <2.10 mmol/L, irrespective of clinical significance. Such events occurred with similar incidences across treatment groups (8.4%, 6.4% and 10.5% for GP2411, EU-Xgeva and US-Xgeva, respectively). Most events were of grade 1 severity and no events of grade 3 or 4 occurred.

The overall incidence of AEs suspected to be related to study drug by the investigator was similar across treatment groups. Again, imbalances on SOC level occurred between the GP2411 and US-Xgeva group, but these were less pronounced for study drug related AEs than for overall AEs. None of the AEs suspected to be related to study medication was of grade 3 or 4.

Three subjects experienced ISRs during Study 101, all of which were grade 1 in severity.

Overall, the safety findings of Study 101 were in line with the known safety profile of Xgeva (Xgeva SmPC and Xgeva USPI).

In Study 301, the percentage of subjects who experienced at least one AE in TP1 was lower in the GP2411 group compared to the EU-Prolia group (59.7% and 68.6%, respectively). Overall, the most frequently reported AEs by PT were hypocalcaemia (10.6% and 9.8% for GP2411 and EU-Prolia, respectively) and nasopharyngitis (8.7% and 6.1% for GP2411 and EU-Prolia, respectively), both occurring with similar incidences in both treatment groups. All cases of hypocalcaemia were grade 1 or 2 and none of the subjects showed clinical symptoms associated with hypocalcaemia.

Despite the overall imbalance in the number and percentage of AEs between groups, imbalances on SOC and PT level were only apparent for 'Infections and infestations' when comparing AEs that occurred in at least 3% of subjects in any treatment group (24.3% and 28.8% for GP2411 and EU-Prolia, respectively). Also, the

percentage of subjects with AEs considered as treatment related in TP1 was lower in the GP2411 group than in the EU-Prolia group (13.7% and 18.6%, respectively). However, none of these events was higher than grade 2.

Imbalances in the overall percentage of AEs were also noted between treatment groups in TP2 (26.9%, 37.6% and 38.7% in the GP2411, EU-Prolia and EU-Prolia/GP2411 switch group, respectively). The most frequent AEs on PT level across all treatment groups were COVID-19 infection, nasopharyngitis, and arthralgia. The overall incidence of AEs with a suspected causal relationship to study drug was low but imbalances were observed between the three treatment groups (GP2411/GP2411: 2.8%, EU-Prolia/EU-Prolia: 5.6%, and EU- Prolia/GP2411: 4.0%) during TP2. All treatment related AEs were of grade 1 or 2.

Although there have been minor imbalances of TEAEs between the treatment groups in TP1 as well as in TP2, none of them revealed any trend or pattern, and no single event predominated. Therefore, the differences are not considered clinically significant nor were the reported events unexpected in light of the established safety profile of denosumab.

In Study 301, one subject in the GP2411 treatment group died on study day 175 during TP1 (PT: sudden death). She had received one dose of GP2411 on study day 1. This subject had a medical history of several underlying cardiovascular conditions, including hypertension and was treated with several concomitant medications. Her ECG examinations performed on Day 1 and Day 8) were assessed as abnormal but not clinically significant. The exact cause of the death was unknown, and no autopsy was performed. Of note, the death was not considered to be related to study drug by the investigator. Despite the lack of information about the exact cause of death, but in light of the overall low incidence of serious AEs, this event is regarded a chance finding.

The percentage of subjects with at least one serious AE was higher in the GP2411 group compared to the EU-Prolia group during TP1 of Study 301 (4.6% and 3.0%, respectively). Of note, under serious AEs it is reported that 4 AEs of non-vertebral fracture occurred in the GP2411 group compared to none in the reference group. Three of these events were grade 3 or 4 in severity. In total, 2 events of hip fracture, one ankle fracture and one femoral neck fracture occurred in the GP2411 group (Source: 5.3.5.1-301 Table 12-9). Additionally, one AE of a grade 3/4 hip fracture was reported in TP2 in the GP2411 group as opposed to none in the reference group (Source: Table 14.3.1-3.3.2). However, none of the SAEs was considered related to study treatment, nor did they lead to study or treatment discontinuations and the patients recovered from these events. Thus, from a safety perspective, no concerns arise on the minor numerical imbalances in non-vertebral fractures between groups.

An imbalance in vertebral fractures was observed during TP1 of Study 301. The incidence of new vertebral fractures was 5.7% in the GP2411 group compared to 9.1% in the reference group. The majority of the new vertebral fractures were mild with a maximum Genant score of 1 and numerically less events occurred in the test group. Further, clinical symptoms such as ‘back pain’ and ‘spinal pain’ were only reported for 1 subject (of 24 with new fractures) in the Prolia group, and for 2 subjects (of 15 with new fractures) in the GP2411 group, i.e. most of the radiographically diagnosed new vertebral fractures did not cause clinical symptoms. Thus, no concern arises from the observed imbalance in new vertebral fractures between treatment groups in Study 301.

Further, there was a higher incidence in new vertebral fractures observed in Study 301 compared to the historical data with the originator (FREEDOM trial). This may be attributable to the following factors: The incidence of prevalent vertebral fractures at baseline in Study 301 was 46.8% in the GP2411 group and 43.9% in the EU-Prolia group. These rates are approximately twice as high as the incidence reported in the

FREEDOM trial with 23.8% in the denosumab arm. According to literature, existence of a previous vertebral fracture is a strong predictive factor for the development of subsequent vertebral fractures (Balasubramanian et al 2019; Genant at al 2000). Therefore, the much higher rate of prevalent vertebral fractures at baseline is considered a relevant cause for the higher incidence of new vertebral fractures during Study 301 compared to the FREEDOM trial. Another contributing factor to the higher incidence of new fractures in Study 301 could be the differences in T-score between Study 301 and the FREEDOM trial. Baseline T-scores were -3.11 (0.42) in the GP2411 group and -3.09 (0.39) in the EU-Prolia group as compared to - 2.82 (0.70) in the denosumab arm in the FREEDOM trial. Lastly, it is assumed that a general improvement in the quality of the radiographs and in their digital transmission over the years facilitated the detection of vertebral fractures in Study 301.

The incidence and nature of SAEs was similar across all treatment groups in TP2. Overall, the incidence was low and there were no SAEs with a suspected causal relationship to study drug during TP2.

Injection site reactions were overall infrequent in both studies and no imbalances between groups were apparent. In Study 301, 18 subjects experienced ISRs (17 in TP1 and 1 in TP2); the proportion of subjects reporting ISRs was similar between the two treatment groups during TP1. All ISRs were grades 1 or 2 in severity.

To analyse the potential impact of AdAs/NAbs on safety, AEs of "hypersensitivity" and "anaphylactic reaction" were screened in the reported AEs in Study 301. As a result, 5 events were obtained but none of them was related to the presence of ADA. In conclusion, there were no ADA associated hypersensitivity reactions in any of the treatment groups, including subjects who underwent the switch from EU-Prolia to GP2411.

Immunogenicity

The evaluation of immunogenicity in clinical studies 101 and 301 followed a multi-tiered approach and has been validated using matrices from healthy volunteers and PMO (post-menopausal osteoporosis) patient sera.

The Applicant has adopted an electrochemiluminescence (ECL) bridging immunoassay to screen, confirm and quantify denosumab specific antibodies in human serum of healthy volunteers and patients with PMO. The validation floating screening cut point was estimated in 50 individual serum samples from healthy volunteers and 51 PMO samples and was defined as Blank x NF (1.11 HV; 1.09 PMO). The applicant evaluated the adequacy of the validation cut points in drug naïve baseline serum samples from the clinical studies. As the cut-point resulted in higher screening positive rate than during validation, an in-study screening cut-point was determined based on the drug naïve baseline serum samples (1.20 HV; 1.17 PMO) and used for ADA evaluation of study samples. A conservative approach is generally preferred, as there is risk of missing ADA positive samples. For example, in study GCP24112101, only 1 out of 500 samples had baseline positive samples, when it should have been about 5 out of 500 samples (based on confirmatory cut point with 1% false positive rate). This indicates that the in-study screening (and possibly confirmation) cut-point were not sufficiently conservative. However, as all the ADA positive samples in study GCP24112101 was ADA titer negative, meaning low concentration of ADA, and as the ADA result seemed more accurate in target population (8 out of 525 baseline positive samples), no issues are raised.

In Study 101, the overall incidence of ADA-positive subjects was high, i.e., 57.8%, 64.9% and 69.1% for the GP2411, EU-Xgeva and US-Xgeva group, respectively. However, no subjects were reported as being "ADA titer positive". The number of subjects with persistent ADAs or with NAbs was low and none of the NAb-responses were persistent.

The incidence of ADAs reported in this study was higher in all 3 treatment groups than the overall incidence of <1% reported from historical studies with Xgeva in the Xgeva SmPC and Xgeva USPI. This is considered to be owing to the high sensitivity of the ADA assay used in this study.

All measured samples were reported as "ADA titer negative" meaning that the concentration was below the cut-point for the titer assay (<20 ng/mL) and titers were therefore not quantifiable in any sample.

In TP1 of Study 301 the overall incidence of ADA-positive subjects was high, i.e., 35.4% and 40.9% for the GP2411 and EU-Prolia group, respectively. Only 0.8% of subjects in each treatment group had a positive titer result indicating an overall low immune response to denosumab.

The incidences of ADAs were similar between subjects who switched from EU-Prolia to GP2411 compared with those who continued on EU-Prolia, i.e., 21.0% and 20.8% of subjects in the EU-Prolia/GP2411 and EU-Prolia/EU-Prolia group, respectively. There was no increase in ADA titers, persistent ADA responses or incidence of NAbs after switching from EU-Prolia to GP2411.

To analyse the potential impact of AdAs/NAbs on safety, occurrence of AEs indicative of hypersensitivity or anaphylactic reactions were assessed in Study 301. There were no ADA associated hypersensitivity reactions in any of the treatment groups, including subjects who underwent the switch from EU-Prolia to GP2411.

In conclusion, significantly higher incidences of ADA were found across all treatment groups in the clinical studies conducted for this MAA as compared to historical data from the originator. The Applicant provided a comprehensive discussion on this aspect, demonstrating that the highly sensitive assay used and the frequent sampling were the main reasons for this observation. The incidence of NAb was low and the presence of ADA or NAb did not have a clinical impact on PK, PD, efficacy or safety parameters. Therefore, no concerns arise from the immunogenicity of Jubbonti.

Due to the differences in the incidence of ADAs detected in the submitted studies as compared to the originator studies, the wording for Immunogenicity in SmPC Section 5.1 was revised.

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 69. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hypocalcaemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions

Summary of safety concerns	
	• Atypical femoral fracture • Hypercalcemia in pediatric 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 70. Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Hypocalcemia	Routine risk minimization measures: • SmPC Section 4.4, where recommendation regarding correction and monitoring of calcium levels is provided • SmPC Sections 4.2, 4.3, 4.4 and 4.8 • PL Sections 2, 3 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Skin infection leading to hospitalization	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Osteonecrosis of the jaw	Routine risk minimization measures: • SmPC Section 4.4, where oral hygiene and dental management guidance is provided	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• SmPC Sections 4.4, 4.8 and 5.1 • PL Sections 2 and 4 Additional risk minimization measures: • Patient reminder card	Additional pharmacovigilance activities: • None
Hypersensitivity reactions	Routine risk minimization measures: • SmPC Sections 4.3 and 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Atypical femoral fracture	Routine risk minimization measures: • SmPC Section 4.4, where recommendation for reporting potential symptoms is provided • SmPC Sections 4.4, 4.8 and 5.1 • PL Sections 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	Routine risk minimization measures: • SmPC Sections 4.2, 4.4, 4.8 and 5.1 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important potential risks		
Fracture healing complications	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Infection	Routine risk minimization measures: • SmPC Section 4.8 • PL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Cardiovascular	Routine risk minimization measures:	Routine pharmacovigilance activities beyond

Safety concern	Risk minimization measures	Pharmacovigilance activities
events	• None Additional risk minimization measures: • None	adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Malignancy	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Missing information		
None		

2.7.4. Conclusion

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

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Prolia (EMEA/H/C/001120) and Ziextenzo (EMEA/H/C/004802). The bridging report submitted by the applicant has been found acceptable.

2.9.2. Quick Response (QR) code

A request to include a QR code in the labelling and package leaflet for the purpose of providing partial information of the package leaflet (certain sections) via the website has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

- The website will show all information provided in Annex IIIB of the Product Information.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Jubbonti 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.

Summary of Quality data

The Applicant performed a sound and comprehensive analytical biosimilarity exercise comparing GP2411 60 mg/mL solution for injection, liquid in syringe (Jubbonti, GP2411 LISY) and GP2411 120 mg/1.7 mL solution for injection, liquid in vial (Wyost, GP2411 LIVI) to the EU reference medicinal products (RMP) Prolia and Xgeva, respectively. In addition, data for US-Prolia and -Xgeva are presented. Data for EU-Prolia and -Xgeva have been pooled and the comparison of active-substance related quality attributes was mainly performed with GP2411 active substance. This approach is adequately supported by bridging studies between Prolia and Xgeva or GP2411 active substance and finished product, respectively. A large number of batches/lots, which can be expected to sufficiently reflect product variability of both the proposed biosimilar and the reference product, was analysed. The GP2411 batches/lots have been manufactured according to the clinical or intended commercial process. Comparability of both processes has been demonstrated. Representativeness of the technical active substance batches that were manufactured according to the clinical process at a different facility is sufficiently justified.

In accordance with the Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017) the similarity condition (population in population approach), potential exemptions from this condition, and the operating characteristics of the approach have been discussed by the applicant. The Applicant generally applied quality ranges based on mean ± X SD with the requirement that at least a certain percentageof the results for GP2411 are within the quality range for

that attribute. Under consideration of criticality of the quality attribute (QA), risk of the QA, analytical method (variability, multiple methods for same QA), data distribution, the observed quality shift for the RMPs, and scientific considerations the multiplier X was adjusted accordingly for each individual QA. Overall, the presented approach is adequately justified and considered acceptable. All individual test results of the analytical similarity exercise are provided.

The relevant quality attributes of the denosumab molecule were assessed using a broad panel of orthogonal state-of-the art analytical techniques. Analysis covered primary sequence and higher order structure, variants related to cysteine chemistry, charge, oxidation, glycosylation, or molecular size, and DP related attributes. Functional activity was compared by a large panel of binding assays and cell-based biological assays covering the mode of action for the targeted indications as well as Fc-related functions. Based on the provided information it is concluded that the analytical methods are suitable for the intended purpose.

As part of the analytical similarity exercise an extended characterisation study was performed to further analyse and compare charge variants. In addition, an extensive comparative forced degradation study complements the biosimilarity assessment. These complementary studies are adequately designed to support the conclusion drawn.

Summary of Non-clinical data

Data regarding biosimilarity have been submitted in the Quality part of the dossier. No non-clinical in vitro or in vivo data have been provided for this MAA.

Summary of Clinical data

GP2411 was developed as a biosimilar product to Amgen's denosumab, which is contained in two different products, Prolia and Xgeva, containing the same active ingredient but at two different strengths with two different presentations. Both originator products were used in the clinical development program for the comparative assessment between GP2411 and Amgen's denosumab.

The clinical development program of GP2411 included two clinical studies to demonstrate similarity in PK, PD, efficacy, safety and immunogenicity of GP2411 and the reference products.

Study CGP24112101 was a randomized, double-blind, three-arm, parallel group, single dose study in healthy male subjects to demonstrate similarity in PK, PD, safety and immunogenicity between GP2411, EU-authorized Xgeva and US-licensed Xgeva. The study was conducted at two investigational sites in Germany. Subjects were randomized in a 1:1:1 ratio. After the screening period (up to 5 weeks), subjects received one single dose of 35 mg s.c. of GP2411, EU-authorized Xgeva or US-licensed Xgeva. The follow-up period was 39 weeks. Overall, the design of study CGP24112101 is acceptable and is generally in agreement with previous Scientific Advice received from EMA (EMEA/H/SA/3409/1/2016/III, EMEA/H/SA/3409/2/2017/III, EMEA/H/SA/3409/2/FU/1/2018/III and EMA/SA/0000067538).

Study CGP24112301 was a randomized, double-blind, multicentre, integrated phase I/III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity of GP2411 and EU-authorized Prolia. The study was conducted in 43 study centres in six countries (Bulgaria, Czech Republic, Japan, Poland, Spain and the United States). Subjects were randomized in a 1:1 ratio for the first treatment period (52 weeks). In the second treatment period (week 52-78) subjects receiving EU-Prolia were re-randomized to receive either GP2411 or EU-Prolia. The subjects received in total three s.c. doses of GP2411 or EU-Prolia. Overall, the design of study CGP24112301 is acceptable and is generally in agreement with previous Scientific Advice received from EMA

(EMEA/H/SA/3409/1/2016/III, EMEA/H/SA/3409/2/2017/III, EMEA/H/SA/3409/2/FU/1/2018/III and EMA/SA/0000067538).

3.2. Results supporting biosimilarity

Quality

For most quality attributes including multiple attributes covering the mechanism of action and other functional activities, GP2411 was demonstrated to be highly similar to the reference products EU-Prolia/-Xgeva. The observed minor analytical differences (for various physico-chemical attributes and FcRn binding) have been adequately justified and are not expected to impact clinical performance of GP2411. Further evidence for biosimilarity is provided by the results of a comparative forced degradation study and extended characterisation of charge variants.

The totality of analytical data from the main analytical similarity study, the supportive bridging studies, and the comparative forced degradation study demonstrate that GP2411 (Jubbonti) is highly similar to the EU reference medicinal product Prolia.

Non-clinical

Analytical and functional similarity studies of Jubbonti (GP2411 of Sandoz GmbH) and Prolia are described and discussed in the Quality part of the dossier. No additional non-clinical studies, neither in vitro nor in vivo, were performed.

Clinical

PK/PD

Study CGP24112101

Biosimilarity in pharmacokinetics of GP2411, Xgeva-EU and Xgeva-US was shown in healthy male volunteers in study CGP24112101. The point estimate of the ratio (GP2411/Xgeva-EU) of the geometric mean for AUCinf was 1.09 with the corresponding 90% CI being (1.03; 1.16). The point estimate of the ratio (GP2411/Xgeva-EU) of the geometric mean for AUClast was 1.08 with the corresponding 90% CI being (1.01; 1.14). The point estimate of the ratio (GP2411/Xgeva-EU) of the geometric mean for Cmax was 1.02 with the corresponding 90% CI being (0.97; 1.08). Thus, all primary PK endpoints were met as all results were within the pre-defined equivalence margin of (0.8, 1.25).

Furthermore, similarity in the PK parameters AUCinf, AUClast, Cmax, T1/2, AUC%extrap, Lambda_z and Tmax among the treatment groups GP2411, Xgeva-EU and Xgeva-US was demonstrated. In addition, the mean drug serum concentrations time-profiles were comparable across the three treatment groups, also supporting similarity in PK.

Biosimilarity in pharmacodynamics of GP2411, Xgeva-EU and Xgeva-US was also shown in study CGP24112101. The "AUEC of %CfB in serum CTX" was evaluated as a secondary endpoint. The point estimate of the geometric mean ratio (GP2411/Xgeva-EU) for AUEC was 1.01 with the corresponding 95% CI being (0.96; 1.05). Thus, the 95% CI for the ratio of geometric mean for AUEC of %CfB in serum CTX was within the pre-specified acceptance criteria of 0.8 to 1.25, which supports PD similarity of the test and reference product.

This was further supported by comparable mean %CfB in CTX serum concentration profiles over time for the GP2411, Xgeva-EU and Xgeva-US groups. Additionally, the mean %CfB in PINP serum concentration profiles over time was also similar across the groups.

Study CGP24112301

In study CGP24112301, biosimilarity in pharmacokinetics was demonstrated between GP2411 and EU-Prolia in osteoporosis patients. After the first dose, the point estimate of the ratio (GP2411/EU-Prolia) of the geometric mean for AUCinf was 0.99 with the corresponding 90% CI being (0.93; 1.05). The point estimate of the ratio (GP2411/EU-Prolia) of the geometric mean for Cmax was 0.97 with the corresponding 90% CI being (0.92; 1.03). Thus, after the first dose in osteoporosis patients, the PK parameters AUCinf and Cmax were similar between the GP2411 and the EU-Prolia group.

These results were further supported by the summary statistics of PK parameters which revealed that the AUCinf, mean AUClast mean Cmax, lambda_z and AUC%extrap and T1/2 were similar between the GP2411 and EU-Prolia group. Additionally, the mean drug serum concentration time profiles after the first dose was similar between the treatment groups, thus further supporting the PK similarity in of the test and reference product in the osteoporosis patients.

Biosimilarity in pharmacodynamics was also demonstrated in osteoporosis patients in study CGP24112301. The primary PD endpoint "AUEC of %CfB in CTX" was met. The point estimate of the ratio (GP2411/EU-Prolia) of the geometric mean for AUEC of %CfB in CTX after the first dose was 1.00 with the corresponding 95% CI being [0.98; 1.01]. The primary analysis on the PDS set was further supported by a post-hoc analysis conducted with a modified PD set in order to account for the high number of subjects excluded from the PDS set.

PD similarity was further demonstrated by similar mean %CfB in CTX serum concentration time profiles for the GP2411 and EU-Prolia groups. Moreover, also the %CfB in PINP serum concentration time profiles were comparable between the groups.

Efficacy

Study CGP24112301

The biosimilarity of GP2411 and EU-Prolia in terms of efficacy was demonstrated in osteoporosis patients. The primary efficacy analysis on the %CfB in LS-BMD at Week 52 was performed on the PPS set and revealed that the difference between the GP2411 and the EU-Prolia group was -0.145% with the corresponding 95% CI being -0.796% and 0.509%. Thus, the primary efficacy endpoint was met. The 95% confidence limits (-0.796%; 0.509%) are very well within the pre-defined and accepted equivalence range of [-1.45%, 1.45%] and estimate a 'maximum' difference of 0.796%. This size of a difference between the treatments is thereby convincingly supporting clinical equivalence of the treatments. Additionally, the primary efficacy endpoint analysis was also conducted with the TP1 FAS set supporting the results from the PPS set. Moreover, the applicant provided several sensitivity analyses which also support the primary efficacy endpoint analysis.

Similarity in efficacy was further supported by the secondary efficacy endpoints. The summary statistics of %CfB in BMD at lumbar spine at week 26 and the %CfB in BMD at total hip and femoral neck at week 26 and week 52 showed comparable mean BMD and %CfB between the GP2411 and EU-Prolia group. Additionally, the applicant could demonstrate that there is no difference between those subjects who switched from EU-Prolia to GP2411 and those who continued on EU-Prolia for the third dose, as the week 78 data for the LS-BMD, FN-BMD and TH-BMD were similar among the groups.

Safety

Overall, the safety findings observed in the clinical studies were in line with the Prolia and Xgeva labels. The incidence of severe (grade 3 or 4) AEs as well as of SAEs was generally low. No new or unexpected safety issues arose during the course of the studies.

The overall incidence of AEs was similar across treatment groups in Study 101 in healthy male volunteers, as was the overall incidence of AEs suspected to be related to study drug by the investigator.

In Study 301 in female patients, the incidences of AEs as well as of AEs related to study drug were lower in the GP2411 group compared to the EU-Prolia group.

Hypocalcaemia, a known adverse reaction for Prolia/Xgeva, occurred with similar incidences across treatment groups and across studies. A transient decrease in serum calcium levels was observed in both studies, with no apparent differences in magnitude or temporal patterns between treatment groups.

Immunogenicity

Significantly higher incidences of ADA were found across all treatment groups in the clinical studies conducted for this MAA as compared to historical data from the originator. However, titre levels were low in the majority of samples and it was demonstrated that the highly sensitive assay used and the frequent sampling were the main reasons for this observation. The incidence of NAb was low and the presence of ADA or NAb did not have a clinical impact on PK, PD, efficacy or safety parameters.

3.3. Uncertainties and limitations about biosimilarity

Quality

Binding of GP2411 AS to FcRn was at the lower end of the range observed for the RMP which could have an impact on PK. This finding can be attributed to slight differences in the matrix of the GP2411 AS and the SPR assay set-up. Indeed binding of five GP2411 DP lots tested was well comparable to the RMP. Minor differences were observed for various physico-chemical attributes of GP2411. However, a relevant impact on clinical performance is not expected.

Non-clinical

In vitro or *in vivo* studies have not been submitted in the non-clinical part of the dossier.

Clinical

PK/PD

Study CGP24112101

Regarding the PK similarity in study CGP24112101, there were remaining uncertainties on the number of protocol deviations that was different between the groups and for which no obvious explanation was provided. The Applicant outlined that from their point of view the higher number of protocol deviations in the Xgeva-EU group might be a chance finding. Indeed, it is agreed to the applicant that the observed increase in the number of protocol deviations in the Xgeva-EU group might be due to an additive effect of small increases in several protocol deviations and might indeed be a chance finding.

Further uncertainty is derived from the analysis of the pharmacodynamic parameter "rebound area" (area under the response curve that is above 0) in this study, which was quite different among the treatment

groups. The mean rebound area was 522 %*day, 793 %*day and 566 %*day for the GP2411, Xgeva-EU and Xgeva-US group, respectively. The serum CTX values crossed the baseline in only 49 subjects of the GP2411 group, 63 subjects of the Xgeva-EU group and 61 subjects of the Xgeva-US group. Thus, due to the high variability and the low number of subjects crossing baseline, these results are difficult to interpret. The rebound area does not seem to be a very sensitive parameter to be used in the overall similarity setting.

Study CGP24112301

The summary statistics of PK parameters revealed that the median Tmax was 13.0 days for the GP2411 group and 9.94 days for the EU-Prolia group. Thus, the Tmax was quite different between the groups. While the Tmax in the EU-Prolia group was similar to what has been observed in study CGP24112101, the Tmax in the GP2411 group of study CGP24112301 was divergent. However, this might have been due to the less frequent sampling around Cmax in study CGP24112301. Thus, Tmax might not have been sensitively assessed in this study.

Regarding the PD similarity drawn from study CGP24112301, there is an uncertainty concerning the definition of the PD parameter rebound area. However, due to the very low number of patients returning to CTX baseline after the first dose in study CGP24112301, an alternative definition for AUEC and rebound area is not regarded necessary for study CGP24112301.

There is an imbalance in subjects excluded from the PDS set (13.3% excluded in the GP2411 group and 19.3% excluded in the EU-Prolia group), which was mainly driven by the reason "required visit samples are missing or excluded" (5.3% in the GP2411 group and 10.2% in the EU-Prolia group). Detailed listing shows that the reason "Visit 2 concentration non-fasting or time window violation" is responsible for the imbalance between the groups (GP2411: 1.5% and EU-Prolia: 6.4%). An explanation for this imbalance was not provided and was requested. The Applicant could not provide an explanation for the imbalance at visit 2 but notes that visit 2 occurred prior to the double-blind scheduled treatment was given and therefore no link to randomized treatment assignment can be made. Thus, the applicant considers it a chance finding. In addition, the applicant provided the requested details on the time window violations for the whole study. The total number of subjects with time window or fasting violations was 14 in the GP2411 group and 22 in the Prolia group. At the sample level, the frequency of deviations was low (0.7% of 1807 GP2411 samples and 1.2% of 1800 EU-Prolia samples). The median time deviations from the allowed time window was 30 min for the GP2411 samples and 30 min for the EU-Prolia samples. Thus, the imbalance between groups in the time window violations at visit 2 might indeed be a chance finding.

The Applicant chose to base the assessment of PD similarity upon the 95% CIs of the ratio of the geometric means (test/reference) for the AUEC of %CfB in serum CTX concentrations, which had to be contained entirely within the pre-specified acceptance margin of [0.8000, 1.2500]. The 95% confidence limits (0.98; 1.01) were close enough to 1 and estimate a 'maximum' difference of 2%. This size of a difference between the treatments is considered clinically not relevant and is thereby convincingly supporting equivalence of the treatments. No further justification on the predefined equivalence range is needed.

Efficacy

Study CGP24112301

According to a table describing the relevant medical histories and current medical conditions for the TP1 SAF set, osteoporosis is present in only 28.1% of the GP2411 group and 31.1% of the EU-Prolia group. In addition, menopause and post-menopause apply to only 8.4% and 3.4% of the GP2411 group, respectively, and to 12.1% and 4.2% of the EU-Prolia group. This is counterintuitive, as the in- and exclusion criteria were

chosen to recruit a population of postmenopausal women with a diagnosis of osteoporosis. Thus, the applicant was asked to clarify and justify if the recruited population is indeed representative for a population of post-menopausal women with osteoporosis. The Applicant confirmed that in line with the inclusion criteria 2 and 5, all subjects enrolled in study 301 were post-menopausal women with osteoporosis. The discrepancy in the abovementioned table of the CSR was due to data erroneously entered on the Medical History CRF page for some subjects. Although the CRF Completion Guidelines instructed investigators not to enter the diagnosis or symptoms under investigation or any condition related to menopause/post-menopause, some investigators did not follow these guidelines.

Regarding statistical methods, the model for the primary endpoint %CfB in LS-BMD did not include all stratification factors used at randomisation. Analyses performed by the rapporteur based on submitted raw data showed that the statistical model including all stratification factors did not alter the study conclusion.

Safety

Imbalances between groups occurred in the number of new vertebral fractions in Study CGP24112301. However, the majority of new vertebral fractures were mild and numerically less events occurred in the test group. Further, there was a higher incidence of new vertebral fractures observed in Study 301 as compared to the historical data with the originator. This may be explained by differences between studies with regard to prevalence of vertebral fractures at baseline, different T-scores at baseline, and a general improvement in the quality of the detection methods over the years.

Slight imbalances were observed in the incidence of serious and grade 3 or 4 non-vertebral fractures between the GP2411 and Prolia groups. However, none of the SAEs was considered related to study treatment, nor did they lead to study or treatment discontinuations and the patients recovered from these events.

3.4. Discussion on biosimilarity

The totality of analytical data from the main analytical similarity study, the supportive bridging studies, the extended characterisation study, and the comparative forced degradation study demonstrate that the applicant's denosumab GP2411 is highly similar to the RMPs EU-Prolia and -Xgeva. The minor differences observed for various physico-chemical attributes and FcRn binding of GP2411 AS are not expected to impact clinical performance of GP2411.

In study CGP24112101 conducted in healthy male volunteers with the 35 mg dose, PK biosimilarity was formally demonstrated among GP2411, Xgeva-EU and Xgeva-US. For the primary PK parameters AUCinf, Cmax and AUClast the 90% CI for the ratio of the test and reference product fell within the prespecified acceptance range of 80.00-125.00%. Thus, all primary PK endpoints from this study were met. This was supported by similar summary statistic of other PK parameters in this study. PK data from study CGP24112301 conducted in female osteoporosis patients with the 60 mg dose further supported PK similarity of the test and reference product. In study CGP24112301, the point estimate of the ratio (GP2411/EU-Prolia) of the geometric mean with the corresponding 90% CI for AUCinf and Cmax was within the pre-specified equivalence margin. These results were further supported by the summary statistics of other PK parameters.

PD similarity has also been demonstrated in both clinical studies. In study CGP24112101, the 95% CI for the ratio of geometric mean for AUEC of %CfB in serum CTX was within the pre-specified acceptance criteria of 0.8 to 1.25. This was further supported by comparable mean %CfB in CTX/PINP serum concentration profiles over time. However, the analysis of the pharmacodynamic parameter "rebound area" showed differences between the treatment groups, which are currently difficult to interpret. In study CGP24112301, biosimilarity

in pharmacodynamics was demonstrated in female osteoporosis patients. The primary PD endpoint "AUEC of %CfB in CTX" was met, as the geometric mean for AUEC with the corresponding 95% CI was within the pre-specified acceptance range of 0.8 to 1.25.

Similarity regarding efficacy was shown in study CGP24112301. The primary efficacy analysis on the %CfB in LS-BMD at Week 52 for the EMA was performed on the PPS set and revealed that the difference between the GP2411 and the EU-Prolia group with the corresponding 95% CI was within the pre-specified margin. The difference between the GP2411 and the EU-Prolia group was -0.145% with the corresponding 95% CI being -0.796% and 0.509%. The 95% confidence limits (-0.796%; 0.509%) are very well within the pre-defined and accepted equivalence range of [-1.45%, 1.45%] and estimate a 'maximum' difference of 0.796%. This size of a difference between the treatments is thereby convincingly supporting clinical equivalence of the treatments. Additionally, the primary efficacy endpoint analysis was also conducted with the TP1 FAS set supporting the results from the PPS set.

Based on the provided safety and immunogenicity data, the safety profile of GP2411 is comparable to that of the originator. No unexpected safety concerns were detected across the clinical studies and the observed safety findings correspond to the known safety profile of the reference products Prolia and Xgeva.

Overall, from a clinical point of view, a well-established biosimilarity exercise has been conducted, which confirms biosimilarity of the test and reference product.

3.5. Extrapolation of safety and efficacy

GP2411 was developed as a biosimilar product to Prolia. 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 generalized 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.

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 GP2411 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, Jubbonti 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 that the benefit-risk balance of Jubbonti 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.