25 April 2025
EMA/165411/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Yaxwer

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/006437/0000

Note

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

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List of abbreviations

AEX	Anion Exchange Chromatography
AC	Acceptance Criterion
AGE	Advanced Glycation End products
BET	Bacterial endotoxin test
BP	Bubble Point
CEX	Cation Exchange Chromatography
CFU	Colony Forming Unit
CHO	Chinese hamster ovary
cIEF	capillary Iso-electric Focusing
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
ELISA	Enzyme Linked Immunosorbent Assay
EoSL	End of Shelf life
GPP	General Process parameter
GR	Gedeon Richter Plc.
HC	Heavy Chain
HILIC-UHPLC-FL	Hydrophobic Interaction Chromatography-Ultra HPLC with Fluorescence
HMW	High Molecular Weight Species
HPLC	High Performance Liquid Chromatography
IND	International New Drug
IPC	In-process Control
IPM	In-Process Monitoring
LC	Light Chain
LMW	Low Molecular Weight Species
MCB	Master Cell Bank
Met253	Methionine in the 253 position
MFI	Micro Flow Imaging
N/A	Not Applicable
NMT	Not More Than
NOR	Normal Operating Range
PAR	Proven Acceptable Range
PCEs	Process Control Elements
pDADMAC	Poly (diallyldimethylammonium chloride)
Ph. Eur.	European Pharmacopeia
PPI	Process performance indicator
PPP	Process performance parameter
PPQ	Process Performance Qualification
PV	Process Validation
QA	Quality Attribute
QTPP	Quality Target Product Profile
R&D	Research and Development
RANKL	Receptor Activator of Nuclear Factor kappa-B Ligand
R-CE-SDS	Reducing Capillary Electrophoresis Sodium Dodecyl Sulfate
RGB-14-P	Denosumab 60 mg Injection in Pre-filled Syringe
RGB-14-X	Denosumab 120 mg Injection
RMP	Reference Medicinal Product
RNS	Rigid Needle Shield
RP-HPLC	Reversed-phase HPLC
RP-HPLC-UV	RP-HPLC UV detector
SEC	Size-exclusion chromatography
SE-HPLC	Size-exclusion-HPLC
SOP	Standard Operating Procedure
TPP	Target Product Profile

WFI	Water for Injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gedeon Richter Plc. submitted on 27 June 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Yaxwer, 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:

- Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone (see section 5.1).
- Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

1.2. Legal basis, dossier content and multiples

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.

This application is submitted as a multiple of Junod simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004.

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: Xgeva 120 mg solution for injection
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 13-07-2011
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/11/703

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

- Product name, strength, pharmaceutical form: Xgeva 120 mg solution for injection
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 13-07-2011
- Marketing authorisation granted by:
  - Union

- Marketing authorisation number: EU/1/11/703

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

- Product name, strength, pharmaceutical form: Xgeva 120 mg solution for injection in vial
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 13-07-2011
- Marketing authorisation granted by:
  - Union

  Marketing authorisation number(s): EU/1/11/703
- Bioavailability study number(s): RGB-14-001

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
17 April 2019	EMA/CHMP/SAWP/338801/2019	Elina Rönnemaa, Juha Kolehmainen
28 May 2020	EMA/CHMP/SAWP/260988/2020	Ferran Torres, Sheila Killalea

The scientific advice pertained to quality and clinical aspects.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Thalia Marie Estrup Blicher

The application was received by the EMA on	28 June 2024
The procedure started on	18 July 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 October 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 October 2024
The CHMP Co-Rapporteur's Critique was circulated to all PRAC and CHMP members on	21 October 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 November 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 February 2025
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	01 April 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 April 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Yaxwer on	25 April 2025

2. Scientific discussion

2.1. About the product

Yaxwer (RGB-14-X) was developed as a biosimilar medicinal product to Xgeva. Xgeva contains denosumab as active pharmaceutical ingredient.

Denosumab targets and binds with high affinity and specificity to human receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone, and cancer-induced bone destruction.

Yaxwer contains the same amount and concentration of drug substance as the reference medicinal product, Xgeva, and is supplied as 120 mg solution for injection in vials.

Yaxwer is intended for all approved indications of Xgeva.

2.2. Type of application and aspects on development

Junod (RGB-14-P) and Yaxwer (RGB-14-X) are proposed biosimilars to EU-Prolia and EU-Xgeva. The applicant has applied for two denosumab biosimilars, Junod (60 mg denosumab, biosimilar to Prolia) and the present Yaxwer (120 mg denosumab, biosimilar to Xgeva). The clinical package for the application of Yaxwer is based on extrapolation of efficacy and safety data from a clinical study conducted in post-menopausal women with osteoporosis and part of the clinical package for the Junod application.

The development has been conducted in line with EMA guidance documents for biosimilars. A comprehensive analytical comparability study according to EMA/CHMP/BWP/247713/2012 has been performed supporting the biosimilarity claim.

The clinical development programme comprises two trials:

- A randomised, double-blind, single, 60 mg fixed dose, parallel comparative pharmacokinetic and pharmacodynamic (Phase I) study of RGB-14-X and US-sourced Xgeva in healthy adult male subjects (protocol number: **RGB-14-001**)
- A randomised, double-blind, multicentre Phase III study to assess the efficacy and safety of RGB-14-P compared to US-sourced Prolia in women with postmenopausal osteoporosis (protocol number: **RGB-14-101**)

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as solution for injection in a vial containing 120 mg of denosumab as active substance.

Other ingredients are: Acetic acid glacial, Sodium hydroxide (for pH adjustment), Sorbitol (E420), Polysorbate 20, Water for injections.

The product is available in a clear glass injection vial (Type I glass) sealed with bromobutyl rubber stopper covered with a fluorinated coating and a plastic flip cap with aluminium sealing.

2.3.2. Active substance

2.3.2.1. General information

Denosumab is a human monoclonal IgG2 antibody heterotetramer, consisting of 2 heavy chains of the gamma 2 subclass (448 amino acids per chain) and 2 light chains of the kappa subclass (215 amino acids per chain). The molecular weight of the glycosylated molecule is ~148 kDa. Denosumab is produced in a mammalian cell line (Chinese hamster ovary cells) by recombinant DNA technology. Denosumab has three major disulfide isoforms. Each heavy chains contains one N-linked glycan, comprising of biantennary structures. The carbohydrate moiety is linked to asparagine at position 298 on the heavy chains.

The function of denosumab is to inhibit the formation, function, and survival of osteoclasts by blocking the RANKL/RANK (Receptor Activator of Nuclear Factor kappa-B Ligand) interaction, thereby reducing bone resorption in cortical and trabecular bone.

2.3.2.2. Manufacture, characterisation and process controls

The manufacturing of the active substance, finished product and batch release takes place in Chemical Works of Gedeon Richter Plc.(Gedeon Richter Plc.) Richter Gedeon utca 20., Debrecen, 4031, Hungary. The applicant provided a valid EU GMP certificate for this site.

Description of manufacturing process and process controls

Denosumab active substance manufacturing process has been adequately described. Main steps are thawing of vials of working cell bank, expansion, centrifugation, flocculation of the produced cell culture, clarification of the bulk harvest by depth filtration and microfiltration. The downstream purification process begins with affinity chromatography, viral inactivation, exchange chromatography, viral filtration and ends with bulk filtration and filling. The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxins, are described for each step. The active substance manufacturing process is considered acceptable.

RGB-14 (company code) active substance is produced in a mammalian cell line (Chinese hamster ovary cells, CHO DG44) by standard recombinant DNA technology. Batch and scale definitions were provided. Each batch of RGB-14 active substance receives a unique batch number which provides traceability to the manufacture.

The applicant divides the active substance manufacturing process into three parts: upstream, midstream and downstream process.

RGB-14 active substance is expressed in Chinese hamster ovary (CHO) cells. The cell culture process starts with the thawing of two vials of the Working Cell Bank (WCB) followed by several expansion steps.

The midstream process starts with the removal of cells and cell debris from the produced cell culture broth using standard separation and clarification techniques. Finally, the supernatant undergoes depth filtration and microfiltration.

The AS is captured and purified from the micro-filtered cell culture fluid through a series of capture and polishing chromatography steps. Subsequently, an ultrafiltration step is performed using an ultrafiltration system to transfer the AS into formulation buffer and adjust the concentration of it. At the end of the downstream process, the formulated AS solution is filtered into bags. Microfiltration of the active substance is carried out using a single 0.2 µm pore size filter.

Filling is followed by aseptic sampling from each bag into primary packaging bags. Denosumab filled into these primary packaging bags are then placed into secondary packagingand finally into pool boxes which are then labelled and the freezing procedure is started.

The manufacturing process also includes dedicated, orthogonal virus clearance steps, i.e. low pH virus inactivation, virus removal through chromatography step and virus filtration using a virus reduction filter.

The description of the manufacturing process steps is accompanied by flow charts indicating the process parameters and process controls.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

Raw materials, reagents and solvents

Raw materials used for the cell culture and purification process are listed together with their quality standard (non-compendial, Ph. Eur., USP) and their intended use. For the non-compendial raw materials applicable in-house specifications are listed. The applicant states that there are no materials of direct animal origin used in the manufacture, with the exception of galactose derived from bovine milk. For the milk derived galactose, certificate of origin is presented.

The composition of the cell culture media and feed solutions are listed.

Source, History and Generation of the cell Substrate

The host cell line used for the production is derived from Chinese Hamster (Cricetulus griseus) Ovarian cells (CHO DG44). Cell bank viability and a test for identity were performed, and the cell bank was characterised to assure the absence of microbial contaminants, endogenous and adventitious agents. Representative images for the lead clones were provided. The target amino acid sequence used for denosumab was compared to the Drugbank sequence. Moreover, the amino acid sequence of the product was verified by orthogonal sequencing methods of intact chains and isolated peptides

Cell banking system, characterisation and testing

A two-tiered cell banking system was created, in which the MCB (Master Cell Bank) was first established and then used to generate the WCB (Working Cell Bank). The cell banking system is adequately described with details on manufacture and storage of the MCB and WCB. The MCB was extensively tested in vitro and in vivo for the presence of adventitious viruses and for various specific viruses and retroviruses. In addition, a real-time PCR assay was conducted for specific detection of MVM-DNA sequences. An EPCB (End of Production Cell Bank) was established.

Also, the EPCB was characterised to confirm species identity, gene copy number, sequence, heavy chain and light chain gene integration sites, and integrity of the transcript. The results confirm the cell line species and that the correct coding sequence is present in the EPCB.

A summary of the protocol for the establishment of future WCBs is provided separately.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the Denosumab active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Control of critical steps and intermediates

The control strategy includes in-process controls (IPCs), in-process monitors (IPMs) and critical process parameters (CPPs). The risk score for establishing preliminary Critical Quality Attributes is presented and found acceptable.

The unprocessed bulk has been identified as critical intermediate. Control of the unprocessed bulk described adequately.

Tabulated summaries for in-process controls and monitors are provided for each process step. The basis of categorisation, the risk scoring method and the justification of the final categorisation of the individual QAs (Quality Attributes) is presented.

Hold times and relative temperatures are listed. Main IPC methods are described.

A summary of reports with method description and results used for testing the unprocessed bulk harvest is provided, together with reference to the correspondent Annexes. The results of the CPPs and IPCs of commercial scale active substance batches are presented and found acceptable.

Process validation .

Denosumab active substance manufacturing process has been validated adequately. Overall, the results indicate consistency of the process. For the PPQs batches the results met the pre-specified acceptance criteria (AC) and were included in the range.

Hold time studies for USP media, DSP buffers and process intermediates were also performed at scale for three PV batches and found acceptable.

Extractables and leachables studies:

Potential extractable components were evaluated according to the relevant guidances.

All calculated PDE (Permitted Daily Exposure) levels were below the permitted levels, indicating that there are no safety concerns due to potential leachables in RGB-14 active substance. Therefore, no leachables study was performed.

Bulk-scale frozen storage development:

The effect of freezing and thawing on the quality of the active substance were evaluated. No major changes were noticed.

Transport validation was performed in summer and winter conditions, with acceptable results.

Manufacturing process development

The manufacturing process development has been described in sufficient detail.

Description of the overall process control strategy:

Overall, the control strategy is adequately described. Definitions and attributions of CQA/CPP/PPP/GPP/IPC/PPI/IPM are generally acceptable.

Characterisation

Denosumab active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure. The analytical results are consistent with the proposed structure.

Elucidation of structure and other characteristics

The applicant presented characterisation data on sufficient number of representative active substance and finished product batches using orthogonal, state-of-the-art analytical methods Descriptions of the analytical methods and qualification/validation reports are

The amino acid sequence was experimentally confirmed by multiple reduced peptide mapping measurements Moreover, analysis of disulphide bond distribution and isoforms, as well as analysis of free thiols groups were also performed. Higher order structure was also characterised. The presence of post-translational modifications and alterations was sufficiently assessed. Also, the functional characterisation was sufficiently addressed and included binding assays, as well as functional assays. Reference is also made to the biosimilarity section.

Impurities

A discussion of the potential impurities in RGB-14 active substance has been provided.

Process-related impurities were divided in biological and media-derived. Clearance to acceptable levels was demonstrated, and risk assessments were performed where relevant, showing compliance with safety thresholds such as permitted daily exposure (PDE). Certain impurities are monitored through release testing or are controlled at the raw material level.

Product-related impurities were further classified into "product variants and "degradation productsFinally, a further class of impurity was defined as "process contaminant", including the following categories: mycoplasma, viral contamination, sterility, bacterial endotoxins and microbiological purity (bioburden).

For relevant "product variants", the biologic activity was characterised using orthogonal methods. Importantly, variants increased or decreased activities remain well within the acceptance criteria. Moreover, their levels are controlled at release and stability, therefore this is considered acceptable.

Degradation products of the active substance has been extensively studied via stress and accelerated conditions. Sufficient information on potential degradation products has been provided.

For the "process contaminants", a table with the type of control strategy was provided and for further information reference to other sections was included.

Regarding the nitrosamine risk assessment, the applicant concludes that for RGB-14, there is no risk of formation of N-nitrosamines and this can be agreed.

2.3.2.3. Specification

The release specification for RGB-14 active substance comprises tests for general attributes (colour, opalescence, visible particles, pH and osmolality), identity, purity/impurity, heterogeneity, quantity, biological activity, potency, and microbiological safety (bacterial endotoxins and bioburden).

Identity is confirmed by appropriate physicochemical methods. Quantity, potency, and purity are assessed using validated analytical techniques. General attributes colour, opalescence, visible particles, pH, and

osmolality as well as microbiological attributes are determined according to compendial methods. In the commercial RGB-14 active substance release and shelf-life specification, three methods are proposed to be omitted, which is found acceptable. Overall, the set of quality attributes tested at release complies with ICH Q6B, and EMA/CHMP/BWP/532517/2008 and is acceptable.

Acceptance criteria have been established based on manufacturing capability, data from the analytical similarity exercise (QTPP (Quality Target Product Profile) ranges), product characterisation data, batch release and stability data, as well as using a statistical approach Sufficient number of representative batches were used to set up specification ranges. Evolution of the specifications throughout development is described.

Overall, the acceptance criteria are considered tight enough to ensure the consistent quality of active substance.

Analytical methods

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

Analytical procedures and method verification/validation/qualification are very extensively described. The data are considered adequate and acceptable.

Batch analysis

Batch analysis data are presented with the commercial process. All results comply with the proposed commercial specifications. In summary, the presented results demonstrate that the manufacturing process reliably delivers active substance with consistent quality.

Reference materials

A two-tiered system for reference material is in place. The reference standards development and qualification were adequately described. The protocol for the qualification of new reference material is considered acceptable.

2.3.2.4. Stability

The stability studies included tests at long term conditions of -40°C ±5°C for up to 36 months from six batches. Furthermore, a study at accelerated conditions of 5°C ±3°C for up to 12 months and stressed conditions of 25 °C ± 2 °C/60% ± 5% RH for six months were performed. The CCS used was the same as for commercial manufacturing.

. Moreover, a photostability study and a freeze-thaw study were also performed. No trends or OOS were identified for the freeze-thaw study, Based on the results of the photostability study, light exposure must be controlled during manufacture and storage of RGB-14 active substance and finished product.

A forced degradation study was performed using finished product batches (see Finished Product section).

The stability specification for active substance does not include process-related impurities, glycosylation, and peptide mapping. For the remaining parameters, the acceptance criteria of the stability specifications are identical to those of the release specifications, which is considered acceptable.

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf-life in the proposed container.

The data presented support the stability claim of 36 months at -40°C ±5°C.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The finished product is presented as solution for injection in a vial containing 120 mg of denosumab as active substance. Other ingredients are: Acetic acid glacial, Sodium hydroxide (for pH adjustment), Sorbitol (E420), Polysorbate 20, Water for injections. The appearance of the finished product is colourless to slightly yellow clear liquid, free from visible particles. The composition of Yaxwer is identical qualitative and quantitatively to the one of the reference medicinal product EU-Xgeva. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The pharmaceutical development of RGB-14 is in general adequately described.

The development of the finished product manufacturing process started with laboratory scale experiments and commercial scale development. Laboratory scale batches were manufactured at the Formulation Development Department at Gedeon Richter's (GR) Budapest site, while commercial scale batches were manufactured at Biotechnology Drug Product Plant, Debrecen. A study investigating common stress conditions (agitation, temperature, freeze-thaw, alkaline, oxidative and UV-stress) was performed.

Sufficient microbial control has been demonstrated.

The finished product container closure system consists of a clear Type I glass injection vial sealed with bromobutyl rubber stopper coated with a fluorinated coating and a plastic flip cap with aluminium sealing. The glass vial and stopper are in immediate contact with the finished product and comply with applicable compendial requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

RGB-14 finished product is provided in a vial format, therefore compatibility with the primary container materials is demonstrated during stability testing. Furthermore, the applicant provided data concerning compatibility with the potential administration devices (syringes, etc.). No incompatibilities have been detected using commonly used plastic syringes.

2.3.3.2. Manufacture of the product and process controls

The FP manufacturing sites and their respective responsibilities are appropriately listed in the dossier. Adequate documentation has been provided to demonstrate GMP compliance.

The batch formula of Yaxwer finished product has been sufficiently provided, including formulas for a minimum and maximum batch size.

The RGB-14 manufacturing process consists of preparation of the formulation buffer, active substance pooling, sterile filtrations, aseptic filling, 100% inspection and release sampling of filled vials. The filled vials are labelled by automatic syringe labelling line. A flow-diagram including material inputs, process parameters and IPCs has been provided. Each step has been further described in sufficient detail.

The control strategy has been described. Control strategy parameters CQA, CPP, IPC have been defined. For microbial controls alert and action limits have been installed.

Media fills have been performed, which support the conclusion that the line is capable to aseptically fill.

The process has been properly validated. All CPPs and IPCs as well as other parameters including additional validation tests complied with the predefined acceptance criteria. The assembly and labelling as well as the secondary packaging process were sufficiently validated.

A filter validation study concerning 0.2 µm membrane filters demonstrated sufficient bacterial contamination retention as well as compatibility with finished product.

Extractable and leachable studies were performed. No extractable/leachable above a value of toxicology concern was identified taking the calculated PDE into account.

Shipping validation was performed. It was confirmed that secondary packaged RGB-14 finished product can maintain product temperature requirements and maintains packaging integrity under physical suitability tests.

In conclusion, the manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

2.3.3.3. Product specification

The release specification for RGB-14 finished product include physical tests (colour, opalescence, visible and sub-visible particles, pH, osmolality, container closure and extractable volume), identity, purity/impurity, quantity, biological activity, and microbiological safety (sterility and bacterial endotoxins). The majority of methods are used to control both the active substance and finished product.

The specifications set for the RGB-14 finished product are adequate.

There are no new impurities identified for the finished product other than the ones defined for the active substance, which is acceptable, given that finished product manufacturing consists mainly on a fill and finish of the active substance material. Visible and sub-visible particles were discussed and the control strategy and data evaluated during development and PPQ batches were presented. The overall control of particles is considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

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

Analytical methods

The compendial analytical methods used to test particulate matter (sub-visible and visible particles), colour, opalescence, pH, and osmolality, were sufficiently verified to demonstrate that each analytical method is suitable for routine control testing of the finished product under the actual conditions of use according to the requirements of the related chapters of the current Ph. Eur. The non-compendial analytical methods, validated for relevant performance characteristics in line with the ICH Topic Q2 (R1) guideline.

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

Batch analysis

Batch release data are provided for RGB-14 finished product manufactured commercial manufacturing process in Gedeon Richter Plc., Biotechnology plant Debrecen.

Batch analysis data from commercial scale batches of the finished product were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

For information on reference standards reference is made to corresponding active substance section, which is considered adequate, as the same materials are used for active substance and finished product. Further information is provided for the reference standards used for bacterial endotoxin and polysorbate 20 testing. The information provided is considered sufficient.

Container closure

The RGB-14 finished product container closure system (CCS) consists of a clear Type I glass injection vial sealed with bromobutyl rubber stopper coated with a fluorinated coating and a plastic flip cap with aluminium sealing. The glass vial and stopper are in immediate contact with the finished product and comply with applicable compendial requirements. The quality control testing is sufficiently described.

Overall, the CCS is considered to provide sufficient finished product protection against microbial contamination and adequate for long-term storage as supported by stability studies performed with identical CCS materials. The control strategy in place for the CCS qualification is sufficient.

2.3.3.4. Stability of the product

A shelf life of 3 years at 2-8 °C is proposed for the finished product.

The RGB-14 finished product stability programme includes sufficient number of baches tested batches (including the PPQ batches). In line with ICH Q5C the batches were tested under long-term (2-8 °C, 36 months), accelerated (25 ± 2 °C/60 ± 5% RH, 6 months) and stress (40 °C/75±5% RH, 3 months) conditions. The batches were tested in the identical container closure system used for commercial product as described in section P.7. Furthermore, a photostability study and periodic short-term stability at 25 °C ± 2 °C/60% ± 5% RH studies were performed.

Based on the data/analytical results provided for long term stability it can be concluded that there have been no changes in the physicochemical attributes or potency of the finished product during the 36-months study. All the tested batches meet the specification when stored at –40 °C ± 5 °C and the results indicate is stable for 36 months. Similarly, under accelerated conditions for 6 months shows no evidence of thermal

degradation. There were no detectable trends in physical changes by any of the physicochemical methods, except for charge variants, and there were no detectable trends in loss of function as measured by the two potency bioassays. There were no detectable trends in physical changes by any of the other physicochemical methods, and there were no detectable trends in loss of function as measured by the two potency bioassays.

The analytical methods used are considered sufficiently sensitive and able to detect the main degradation pathways of RGB-14 finished product. The parameters tested are the same as for release with the exception of extractable volume. Sterility and container closure integrity test by dye ingress decay is included into the stability program, which is adequate.

In order to justify the storage conditions stated in the SmPC/PIL of RGB-14 finished product (at room temperature, i.e., not more than 25 °C ± 2 °C/60% ± 5% RH) for up to 30 days in the original container protected from light a short-term stability study at RT was conducted All specifications were met.

In addition, a photostability study was conducted as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results of the photostability study showed that the RGB-14 finished product in the vial is photosensitive. The packaging material of the marketing pack is expected to offer sufficient protection against light-stress.

No changes have been reported. Furthermore, no increase in sub-visible particles were detected.

The provided post-approval stability protocol is considered sufficient.

Based on available stability data, the shelf-life of 3 years and "Store in a refrigerator (2 °C – 8 °C). Do not freeze. Keep the vial in the outer carton in order to protect from light." as stated in the SmPC are acceptable.

2.3.3.5. Adventitious agents

TSE compliance

Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated. The active substance is produced in a serum-free culture medium. The MCB is free from TSE-risk substances.

Virus safety

The fermentation process of RGB-14 is in a serum-free medium. This minimises a possible contamination for adventitious viruses. The cells used for production of RGB-14 have been extensively screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the MCB, with the exception of intracellular A-type retroviral particles. However, this is acceptable since there is sufficient capacity within the manufacturing process of RGB-14 for reduction of this type of viral particles. The purification process of RGB-14 includes several steps for inactivation/removal of enveloped viruses. The effectiveness of these steps (low pH viral inactivation, chromatography step, small virus retentive filtration) has been sufficiently demonstrated. Viral clearance was demonstrated with a panel of model viruses. During the manufacture of RGB-14 active substance, column chromatography resins are used during purification and reuse has been investigated.

2.3.3.6. Biosimilarity

Analytical Comparability Study

The biosimilarity exercise for RGB-14 followed the recommendations as laid down in EMA/CHMP/BWP/247713/2012.

The main analytical comparability (biosimilarity) study is described in sufficient detail. An adequate number of batches has been included, including EU and US Xgeva, as well as RGB-14 active substance and finished product batches. A risk assessment identified a comprehensive QA list tested during the study. A statistical approach using sample means ± x-time standard deviation was used for quality (biosimilarity) range definition, where appropriate. The approach is in general considered acceptable taking the high number of reference product batches into account. The applicant considered biosimilarity as highly similar if 90% of RGB-14 batches fall into the quality range. This might be acceptable, however every batch outside the quality range needs to be scientifically justified. Furthermore, the applicant considered biosimilarity as similar if 50% of RGB-14 batches fall into the quality range. In this regard, the applicant provided sufficient justifications.

Table 1: Key findings on Biosimilarity

Quality attribute	Analytical method		Evaluation of the similarity		Justification for differences (if any)
			RGB-14-X vs. Xgeva	US vs. EU market	
Composition and strength					
Protein content (API)	UV absorbance		Highly similar	Highly similar	–
Drug product specific QAs					
Subvisible particles (SVP)	MFI		Lower particle number in RGB-14-X than in Xgeva	Higher particle number in US than in EU Xgeva batches	Particles were not considered as target for comparability and USP guidelines were followed. Particle count within USP guidance and lower particle number are considered safer.
	RMM / Archimedes		Lower particle number in RGB-14-X than in Xgeva	Similar	
Product variants, purity					
Size-related variants	SE-HPLC		Highly similar	Highly similar	–
	NR-CE-SDS		Highly similar	Highly similar	–
	AUC		Highly similar	Highly similar	–
Size-related variants	SEC-MALLS		Highly similar	Similar	–

Quality attribute	Analytical method		Evaluation of the similarity		Justification for differences (if any)
			RGB-14-X vs. Xgeva	US vs. EU market	
	R-CE-SDS		Different	Highly similar	Similar HC content for RGB-14-X and Xgeva. Lower NgHC level in RGB-14-X than the EU/US Xgeva QR. No impact on product quality observed as there is no effector function in denosumab. Marginally higher LC+HC content in RGB-14-X than the EU/US Xgeva QR. This correlates with marginally lower NgHC content and marginally higher amount of HC content. The slightly higher LC+HC content is not expected to impact product quality as denosumab has no effector function.
Charge-related variants	cIEF native		Similar	Highly similar	–
	cIEF CPB		Different	Highly similar	Similar levels of acidic and main peak variants for RGB-14-X and Xgeva. Lower levels of basic variants observed in the RGB-14-X batches than the EU/US Xgeva QR. RGB-14-X has a higher level of C-terminal Lys variant. Consequently, the same basic variant level in the two products observed in the native cIEF treatment is reduced more by CPB digestion in RGB-14-X samples. The charge variant enrichment study results revealed the predominance of NgHC in the basic variant species. As Xgeva has a higher level of NgHC, which is enriched in the basic peaks, this is also responsible for the slight difference in the basic variants and correspondingly in the main peak level. However, this ~1% difference has no impact on product quality and clinically not meaningful.
N-Glycosylation pattern	HILIC-UHPLC-FL-FL		Highly similar	Highly similar	–
	InstantPC labelled N-glycans by HILIC-UHPLC-FL-ESI-MS/MS		Similar	Highly similar	–

Quality attribute	Analytical method		Evaluation of the similarity		Justification for differences (if any)
			RGB-14-X vs. Xgeva	US vs. EU market	
Sialic acid	HILIC-UHPLC-FL		Highly similar	Highly similar	–
	RP-HPLC-FL		Similar	Highly similar	–
Disulfide variants	Disulfide isoforms RP-HPLC		Highly similar	Highly similar	–
Oxidation	Focused peptide mapping_RP-HPLC-UV		Similar	Highly similar	–
Glycation analysis	LC-MS		Highly similar	Highly similar	–
Gal-α-1,3-Gal	HILIC-UHPLC-FL/ESI-MS/MS with exoglycosidase digestions		Highly similar	Highly similar	–
Structural variants					
Primary structure, amino acid sequence	LC-MS/MS Lys-C reduced peptide mapping for amino acid sequence confirmation		Identical	Identical	–
	LC-MS/MS Chymotrypsin peptide mapping for amino acid sequence confirmation		Identical	Identical	–
	Molecular weight determination LC-MS		Identical	Identical	–

Quality attribute	Analytical method		Evaluation of the similarity		Justification for differences (if any)
			RGB-14-X vs. Xgeva	US vs. EU market	
Sequence Variants	LC-MS/MS reduced peptide mapping		Different	Highly similar	Two sequence variants were identified in Xgeva but absent in RGB-14.
Disulfide bridges	LC-MS non-reduced peptide mapping		Similar	Highly similar	
Unpaired cysteine			Similar	Highly similar	
Sulfide and trisulfide bonds			Different	Similar	The levels of the same trisulfide bonded peptides were similar for the RGB-14-X drug product and Xgeva RP batches, but sulfide (thioether) bonded peptides were detected in Xgeva products but not in RGB-14-X, which is probably due to the fact that the reference products were stored for longer periods than RGB-14 products at the time of the comparability study. Based on literature data, it is very unlikely that the absence of thioether-bonded minor form would pose a risk in terms of efficacy or safety.
Cysteine related conjugates			Similar	Highly similar	–
Free thiol	Colorimetry (FL)/Ellman's reagent		Highly similar	Highly similar	–
Higher order structure	µDSC		Different	Highly similar	Highly similar level of enthalpy, as well as Tm1 and Tm2 values for RGB-14-X and Xgeva. A slightly lower level of Tm3 results was found in RGB-14 batches than the EU/US Xgeva QR. This slight difference is probably due to the differences in the disulfide isoform distribution between RGB-14 and Xgeva. This lower level of Tm3 has no effect on biological activity and stability.
	FT-IR		Highly similar	Highly similar	–
	HDX-MS		Highly similar	Highly similar	–
	2D NMR		Highly similar	Highly similar	–

Quality attribute	Analytical method		Evaluation of the similarity		Justification for differences (if any)
			RGB-14-X vs. Xgeva	US vs. EU market	
	Far UV CD		Highly similar	Highly similar	–
Post Translational Modification					
Oxidation	LC-MS/MS reduced peptide mapping		Similar	Highly similar	–
Hydroxylation			Different	Highly similar	The same peptides were observed to be hydroxylated in both RGB-14-X and Xgeva. However, the relative abundance of hydroxylation at different sites is observed to be different. Overall, the levels of hydroxylation are lower in RGB-14-X as compared to Xgeva. The level of hydroxylation is negligible for the heavy chain site, and all the other sites are not localised in CDR, therefore no impact on function is expected.
Deamidation			Similar	Highly similar	–
Isomerisation			Highly similar	Highly similar	–
H_2O Loss			Highly similar	Highly similar	–
Modifications of the protein N- and C-termini			Different	Highly similar	Slight differences can be observed in the amount of some modifications of the protein N- and C-termini between RGB-14-X and Xgeva batches. However, the total amount of these modifications is very low and none of these differences are expected to affect antigen binding and PK.
Glycosylation and non-glycosylated HC			Different	Similar	Minor quantitative differences were observed in the relative abundance of some of the glycoforms between RGB-14-X and Xgeva. Most of the differences are marginal and considered negligible. Slight differences in the CQA parameter high mannose species are not critical, as the total high mannose content is similar to Xgeva. The slight differences in the content of complex glycoforms have no effect on efficacy and safety and are therefore not considered critical. Only quantitative differences of three minor glycoforms were found between Xgeva batches from the US and EU markets.
Site specific glycation	LC-MS/MS reduced peptide mapping		Similar	Highly similar	–

Quality attribute	Analytical method		Evaluation of the similarity		Justification for differences (if any)
			RGB-14-X vs. Xgeva	US vs. EU market	
Other variants and unknown peptides			Similar	Highly similar	–
Biological activity					
Target (RANKL) binding	ELISA		Highly similar	Highly similar	–
	BLI		Highly similar	Highly similar	–
	Flow cytometry		Highly similar	Highly similar	–
FcγRIIIa/ CD16a (V158) binding	BLI		Highly similar	Highly similar	–
FcγRIIa/ CD32a (H131) binding	BLI		Highly similar	Highly similar	–
FcγRI/CD 64 binding	BLI		Highly similar	Highly similar	–
FcRn binding	BLI		Highly similar	Highly similar	–
C1q binding	BLI		Highly similar	Highly similar	–
Inhibition of RANKL/ RANK signalling	RANKL neutralisation (DiscoverX Path Hunter)		Highly similar	Highly similar	–
Inhibition of osteoclast differentiation	RAW264.7 cell-based TRAcP5b ELISA		Highly similar	Highly similar	–

Quality attribute	Analytical method	Evaluation of the similarity		Justification for differences (if any)
		RGB-14-X vs. Xgeva	US vs. EU market	
CDC	CDC effector function on IM-9 B RANKL expressing cells	Highly similar	Highly similar	–
ADCC	ADCC effector assay on RANKL expressing cells (Reporter gene assay)	Highly similar	Highly similar	–

Analytical Comparability Results

The protein content, particulate matter and sub-visible particles, size-related variants species by size exclusion chromatography (SE-HPLC) show comparable data between RGB-14 and EU-Xgeva.

For low molecular weight (LMW) species by non-reducing capillary SDS gel-electrophoresis (NR-CE-SDS) slight differences can be seen for LC and HC-HC fragment values. However, the values are low and slightly above the QL (Quantification Limit) of the method.

For size distribution analysis by size exclusion chromatography multi-angle laser light scattering detector (SEC-MALLS) slight differences can be seen for the HMW content and molecular weight. The applicant argues at the EU Xgeva QR (Quality Range) is defined very narrow. Taking the data from the US batches and the overall low values into account this can be accepted.

The RGB-14 batches show lower levels of non-glycosylated HC, hence slightly elevated glycosylated HC measured by R-CE-SDS. As Fc-function are not considered a MoA (mechanism of action) of denosumab these minor differences are not expected to be clinically meaningful. This difference also explains the differences seen for HC, LC and HC-LC values.

The RGB-14 batches show higher levels of the main peak and lower levels of acidic and basic variants in comparison to EU-Xgeva as measured by cIEF. After Carboxypeptidase B treatment the differences were even more pronounced. The applicant argued with a charge variant enrichment study that these differences are not clinically meaningful, which is supported by active substance characterisation data.

Glycosylation

HILIC-UHPLC-FL shows for RGB-14 batches higher levels of terminal galactose and fucosylation in comparison to EU-Xgeva. Given that Fc-effector functions are not part of the MoA of denosumab these differences are considered not clinically meaningful. Furthermore, lower levels of high mannose species were reported. However, the overall difference of about 2% is not considered clinically meaningful as supported by literature.

Further analyses of the glycosylation patterns were performed using HILIC-UHPLC-FL-ESI-MS/MS and RP-HPLC-FL and HILIC-UHPLC-FL methods. Overall, the patterns are comparable with a slight difference in NANA content, which is lower in RGB-14 in comparison to EU-Xgeva. Given the data from the Phase I PK study the differences are considered clinically not meaningful. NGNA, which is a known immunogenic sialic acid species was not detected in EU-Xgeva or RGB-14.

Analyses of the disulphide variants revealed two distinct clusters in the variants of the Xgeva batches (expiry dates 2020 an earlier). The RGB-14 values are similar with the older EU-Xgeva batches. Overall, all RGB-14 batch data fall within the quality ranges of EU-Xgeva.

The RGB-14 values show slightly elevated levels of oxidation. However, the level of oxidation was shown to be stability indicating and impacted by the finished product manufacturing process (light sensitive), which is supported by the data of the finished product batches. Overall, the data show good comparability.

Glycation was analysed using LC-MS analyses. Two distinct clusters were detected for the Xgeva batches. The RGB-14 values fall between both clusters. Overall, all RGB-14 batch data fall within the quality ranges of EU-Xgeva.

Primary structure

The primary structure was determined using several MS-based methods.

The amino acid sequence was verified using Lys-C and chymotryptic peptide mapping experiments. The amino acid sequences of RGB-14 and EU-Xgeva are identical.

Slight differences in oxidation were reported between RGB-14 and EU-Xgeva. Even though the differences are significant for some species they are overall at low levels and outside of the CDR (Complementarity Determining Region). Methionine oxidation can have an effect on FcRn-binding, thereby affecting PK parameters. However, no differences were seen in the PK study.

The hydroxylation pattern of RGB-14 and EU-Xgeva is significantly different. The levels are overall low, and the sites of hydroxylation are outside the CDR. However, structure differences were not seen by other orthogonal methods. Also, in potency assays and the clinical efficacy study no difference was reported. Therefore, the differences are not considered clinically meaningful.

Differences between RGB-14 and EU-Xgeva were seen in deamidation and isomerisation of several sites. The sites were not inside the CDR and the values were overall relatively low. Therefore, the differences are not considered clinically meaningful.

N-terminal and C-terminal analyses revealed slight differences between RGB-14 and EU-Xgeva. RGB-14 shows higher C-terminal lysine, amidation and lower N-terminal pyroglutamate and higher truncated N-terminus. Furthermore, higher levels or carbamylation were detected. Carbamylation was shown to have an effect on CDC, however as this MoA is not relevant for denosumab effectivity the difference is not considered meaningful. C-terminal lysine and N-terminal pyro-gluatmate are known to have no effect on the safety and efficacy of monoclonal antibodies. For the EU- and US-Xgeva N-terminal extensions were detected at low levels. In summary the variant values were overall relatively low and the differences are not considered clinically meaningful.

Site-specific glycosylation mapping was performed by RP-HPLC/ESI-MS/MS analyses as orthogonal method to the HILIC-UHPLC-FL methods. The results are mainly in good agreement with the orthogonal methods. Due to the higher sensitivity slight differences were detected for several structure variants which were mainly detected at very low overall values. In summary, the differences are not considered clinically meaningful.

Sequence variants were detected mainly in EU- and US-Xgeva batches at very low values. In summary the differences are not considered clinically meaningful.

RGB-14 has lower site-specific glycation in comparison to EU- and US-Xgeva. However, none of the detected sites is located in the CDR therefore an effect on binding properties is unlikely. Furthermore, based on prior

knowledge from the literature glycation in the Fc-part is not reported to affect Fc-effector functions. As Fc-effector functions are no MoA of denosumab an effect is highly unlikely. In summary, the differences are not considered clinically meaningful.

Further analyses showed barely detectable differences for minor variants between RGB-14 and EU- and US-Xgeva. In summary, the differences are very minor and not considered clinically meaningful.

The differences detected in the non-reduced peptide mapping analyses for disulphide bridges are well in line with the data obtained using the orthogonal RP-HPLC method. As each isoform detected occurs naturally, differences in the levels of IgG2-A/B isoforms between the two sample groups are not considered a safety concern. The potency assays did also not show any differences. Hence an effect on potency is unlikely.

Some differences were reported between RGB-14 and EU- and US-Xgeva for free cysteines. The data are in good agreement with the already reported differences in IgG2-variants. None of the free cysteines are in the CDR. No effect on thermal stability was reported. Therefore, the differences are not considered clinically meaningful.

The level of trisulfide bonds between RGB-14 and EU- and US-Xgeva were low and overall comparable. Low levels of thioether bonds were detected for EU- and US-Xgeva batches but not RGB-14. In vivo studies in the literature have shown that thioether bonded peptide forms occur during long term storage of IgG1 molecules and the ratio of this modified peptide continues to increase in the human body: thioether levels changes over time in the human circulation. Hence the difference might be attributed to the age of the Xgeva-batches used. However, also one RGB-14 batch with increased age was used. The absence of the thioether bonds is not considered to have an effect on immunogenicity. Therefore, the differences are not considered clinically meaningful.

The levels of cysteine related conjugates showed slightly higher levels of glutathione conjugates and only for RGB-14 homocysteine conjugation. Both conjugates are not considered relevant concerning the safety and efficacy of denosumab. Therefore, the differences are not considered clinically meaningful.

The profile of the deconvoluted mass spectra of the RGB-14 batches is similar to those of the EU- and US-Xgeva batches.

RGB-14 batches and EU- and US-Xgeva batches show similar free thiol contents.

Higher order structure

Investigation of the thermal stability using the µDSC method showed comparable results between RGB-14 batches and EU- and US-Xgeva batches, with the exception of lower TM3 for the RGB-14 batches. This difference is likely due to the higher B isoform levels in Xgeva batches.

Higher-order-structure was further analysed by FT-IR, far UV CD, HDX-MS, and 2D NMR. In summary no significant differences between RGB-14 batches and EU- and US-Xgeva batches were reported.

Biological activity

The binding characteristics to its target (RANKL) were measured. In summary no significant differences between RGB-14 batches and EU- and US-Xgeva batches were reported. In addition, binding to membrane bound RANKL was compared. All RGB-14 batches were within the quality ranges of the EU-Xgeva batches.

Fc-effector functions were compared using BLI methods. Binding to FcγRI, IIa and IIIa were comparable between RGB-14 and EU-Xgeva. C1q binding was also investigated and comparable results received. In summary no significant differences between RGB-14 batches and EU- and US-Xgeva batches were reported.

The binding characteristics to FcRn were compared using BLI methods. In summary no significant differences between RGB-14 batches and EU- and US-Xgeva batches were reported. Furthermore, no differences were seen in the phase I PK study.

The potency of RGB-14 and EU-Xgeva was compared using several cell-based assays. In a RANKL inhibition reporter gene assay and inhibition of osteoclast differentiation measured by cell-based TRAcP5b ELISA both products showed comparable potency. In addition to the FcγR analyses a CDC and an ADCC method were employed. Neither CDC, nor ADCC activity were detected for both products, which was expected.

Forced degradation

Forced degradation studies have been conducted to compare the degradation behaviour of RGB-14 and its reference medicinal product. Stress conditions (temperature, oxidative, pH, and UV stress) were used. In general, the data show comparable results for both molecules.

2.3.4. Discussion 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 development of the active substance and finished product including process characterisation have been sufficiently described.

Concerning the analytical biosimilarity study, it is considered that the batches have been appropriately selected with respect to overall numbers, span of manufacturing dates, and ages at times of testing. The batches were stored under prescribed conditions, and tested within their expiry dates. The criteria for inclusion or exclusion of batches in the individual studies are explained and are found appropriate. The statistical approach and the selection of tests/methods are found acceptable. In general, the data support a conclusion of biosimiliarity. No concern from the quality perspective have been identified.

From a quality point of view the approval of Yaxwer is considered acceptable.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendations for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

To evaluate similarity from a non-clinical perspective, a series of non-GLP comparative in vitro pharmacodynamic studies were performed to compare RGB-14-X/Yaxwer to its reference product Xgeva. The comparability exercise was performed in accordance with relevant EMA guidelines; Guideline on Similar Biological Medicinal Products containing Monoclonal Antibodies – Non-clinical and Clinical Issues (EMA/CHMP/BMWP/403543/2010) and Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMA/CHMP/BMWP/403543/2010.

Denosumab is a human monoclonal antibody (IgG2) and belongs to the 'Drugs for treatment of bone diseases (other drugs affecting bone structure and mineralisation)'. ATC code: M05BX04

Denosumab targets and binds with high affinity and specificity to human receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone, and cancer-induced bone destruction. Fc-effector function (ADCC, CDC, ADCP) are not described for denosumab.

Denosumab has been approved as active substance in Prolia and Xgeva and several biosimilars on the market in the EU.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The primary pharmacology assessment consists of comparative in vitro studies of RGB-14-X with its reference medicinal product (RMP) EU-Xgeva. No in vivo pharmacodynamics animal studies were conducted.

This is in line 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 are considered paramount for the non-clinical biosimilar comparability exercise since they are more specific and sensitive in detecting differences between the biosimilar and the RMP. The functionality in-vitro assays cover all the relevant modes of action claimed in the indications and used representative materials from both RGB-14-X and the RMP. The detected differences are not considered clinically relevant.

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

2.4.2.2. Secondary pharmacodynamic studies

Also the secondary pharmacology assessment consists of comparative in vitro studies of RGB-14-X with its reference medicinal product (RMP) EU-Xgeva. No in vivo pharmacodynamics animal studies were conducted. The absence of Fc-effector functions (ADCC and CDC) has been confirmed. Binding to relevant Fc-γ-Receptors including FcRn was comparable between RGB-14-X and EU-Xgeva.

2.4.2.3. Safety pharmacology programme

As no clinically relevant differences were detected in the analytical comparability study no safety pharmacology studies are expected for RGB-14-X, in line with 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).

2.4.2.4. Pharmacodynamic drug interactions

In line with 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) no pharmacodynamic drug interaction studies are expected.

2.4.3. Pharmacokinetics

Neither stand-alone comparative pharmacokinetics studies nor separate absorption, distribution, metabolism and/or excretion studies were performed with RGB-14-X and EU-Xgeva.

PK similarity was examined in a clinical PK and PD study (RGB-14-001), which is described and discussed in the Clinical section below.

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.

The similarity between the originator and the biosimilar product should have been proven in the frame of the in vitro quality biocomparability testing. In contrast to the in vitro methods, in vivo studies in animals are not considered informative for the similarity / comparability exercise. Due to the high variability, these models are actually too insensitive. This conclusion concerns both pharmacokinetic comparisons and comparisons on safety.

Based on these considerations, the lack of these comparative studies in animal models is acknowledged and accepted.

2.4.4. Toxicology

In line with current guidance (EMEA/CHMP/BMWP/42832/2005 Rev1 guideline), studies regarding toxicology, including developmental and reproductive toxicity studies, are not required for non-clinical testing of biosimilars. Neither are studies regarding safety pharmacology, carcinogenicity and local tolerance. Given the sufficient comparability shown during analytical comparability testing, this is considered acceptable.

2.4.5. Ecotoxicity/environmental risk assessment

"In accordance with Article 8(3) of Directive 2001/83/EC, as amended, the evaluation of the potential environmental risks posed by medicinal products should be submitted, their environmental impact should be assessed and, on a case-by-case basis, specific arrangements to limit the impact should be considered

(Guideline on the environmental risk assessment of medicinal product for human use (EMEA/CHMP/SWP/4447/00 corr 2 issued 01 June 2006)."

And further it is stated, that: "In the case of products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA should be provided. This ERA may consist of a justification for not submitting ERA studies, e.g. due to their nature they are unlikely to result in a significant risk to the environment."

The applicant provided a valid justification for the absence of dedicated ERA studies, which is considered acceptable.

2.4.6. Discussion on non-clinical aspects

The primary pharmacology assessment consists of comparative in vitro studies of RGB-14-X with its reference medicinal product (RMP) EU-Xgeva. No in vivo pharmacodynamics animal studies were conducted.

This is in line 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 are considered paramount for the non-clinical biosimilar comparability exercise since they are more specific and sensitive in detecting differences between the biosimilar and the RMP. The functionality in-vitro assays cover all the relevant modes of action claimed in the indications and used representative materials from both RGB-14-X and the RMP. The detected differences are not considered clinically relevant. Therefore, no further non-clinical in vivo data (PD, PK, toxicology) are considered necessary.

2.4.7. Conclusion on the non-clinical aspects

RGB-14-X is developed as a biosimilar to the reference medicinal product (RMP) EU-Xgeva. Non-clinical evaluation was based on in-vitro assays. These data are discussed in the quality part of the dossier and the assessment is found above. Minor differences were detected which are however justified and not considered clinically relevant. Therefore, no further non-clinical in vivo data (PD, PK, toxicology) are considered necessary. The application is considered approvable from a non-clinical viewpoint.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

- **Tabular overview of clinical studies**

Study No.	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of patients	Primary Objectives
RGB-14-001	Phase 1, double-blind, randomised, single dose, multi-centre, 2-arm, and parallel group study in Healthy male participants. Active controlled.	Single SC injection of RGB-14-X 60 mg (test product) Single SC injection of Xgeva 60 mg (reference product)	165 (RGB-14-X: 83; Xgeva: 82)	To characterize and compare the PK of a single 60 mg SC dose of RGB-14-X with a single 60 mg SC dose of Xgeva in healthy adult male participants.
RGB-14-101	Phase III randomised, double blind, multicentre, multiple fixed dose, two arm parallel group study in patients with PMO. Active controlled.	SC injection of RGB-14-P 60 mg (test product) every 26 weeks SC injection of Prolia 60 mg (reference product) every 26 weeks	Main study phase: 473 (RGB-14-P: 242; Prolia: 231) Transition period phase: 188 (RGP-14-P to RGB-14-P: 63; Prolia to RGB-14-P: 62; Prolia to Prolia: 63)	To demonstrate • similar efficacy and effect of RGB-14-P with US-licensed Prolia on BMD at the lumbar spine at Week 52 in female participants with postmenopausal osteoporosis (PMO) • similar PD (AUEC of %CfB in sCTX) of RGB-14-P with US-licensed Prolia in female participants with PMO

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Bioanalytical methods

Bioanalytical assays were developed and validated for the determination of denosumab serum concentration (PK), determination of sCTX/CTX1 and P1NP serum concentration (PD), detection of anti-denosumab antibodies (ADA) and neutralizing anti-denosumab antibodies (NAb) from serum samples. The assays and their application in the clinical studies are summarised in the table below.

Table 2: Summary of the bioanalytical assays

Method ID	Method title	Analyte	Applicable clinical studies
GLP2015	An electrochemiluminescent method for the quantitative determination of denosumab (RGB-14 and Xgeva) in human serum	Denosumab	RGB-14-001 RGB-14-101

GLP2229	Bioanalytical method for detection of anti-denosumab antibodies from human serum	Anti-denosumab antibodies	RGB-14-001 RGB-14-101
GLP2114	Bioanalytical method for detection of anti-denosumab antibodies from human serum	Anti-denosumab antibodies	Not used
GLP2226	Bioanalytical method for detection of neutralizing anti-denosumab antibodies from human serum	Neutralizing anti-denosumab antibodies	RGB-14-101
1-P-PR-PRO-9000437	Electrochemiluminescence (ECLIA) assay for the analysis of CTX1 in human serum	CTX1	RGB-14-101
1-P-PR-PRO-9000436	Electrochemiluminescence (ECLIA) assay for the analysis of P1NP in human serum	P1NP	RGB-14-101
SCH-AU-STU- ASS-0229-00	Bioanalytical method for determination of sCTX concentration in serum	sCTX	RGB-14-001

Note: Different nomenclature was used in the Phase I and Phase III studies regarding the pharmacodynamic (sCTX/CTX1)

Bioequivalence

Study RGB-X-14-001: Randomised, Double-Blind, Single, 60 mg Fixed Dose, Parallel Comparative Pharmacokinetic and Pharmacodynamic (Phase 1) Study of RGB-14-X and Xgeva in Healthy Adult Male Subjects

Study design

This was a Phase 1, double-blind, randomised, single dose, multi-centre, 2-arm, and parallel-group study. The study evaluated and compared the PK, PD, safety and tolerability, and immunogenicity of a single SC dose of 60 mg of RGB-14-X with the same dose of US-sourced Xgeva in healthy adult male participants. A total of 172 healthy participants aged from 28 to 55 years (inclusive) were planned to be enrolled.

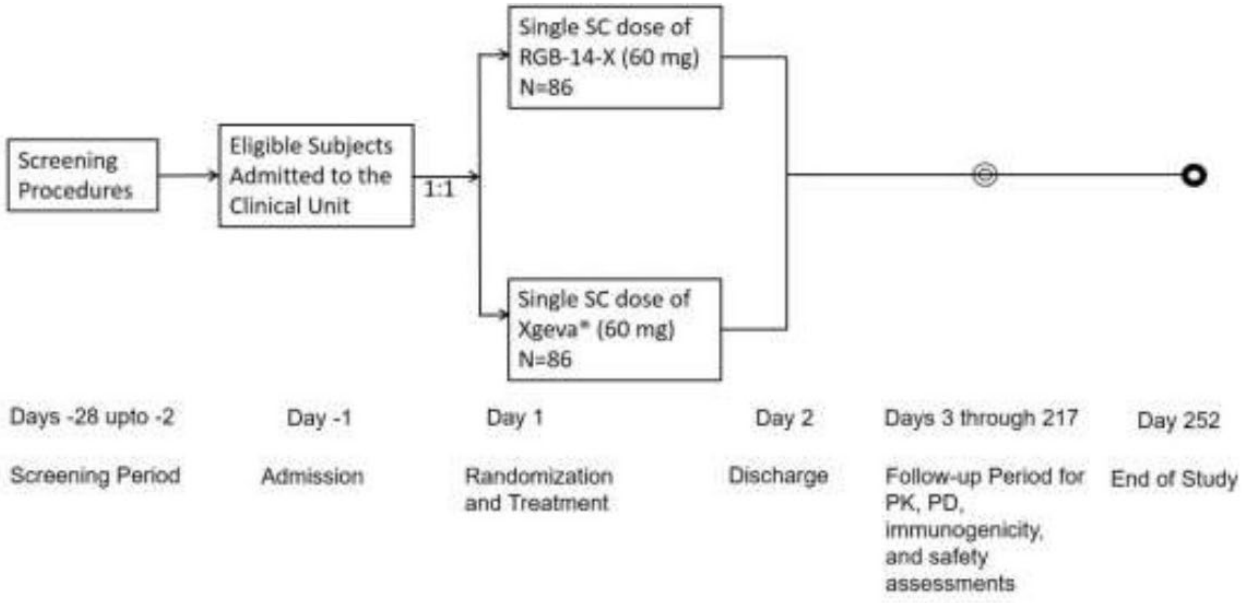
The total duration of study participation for each participant in the study was 40 weeks. The study consisted of a Screening period (up to 28 days), in-house treatment period (2 days), and a follow-up period (250 days). The total confinement period for a participant was 2 days (from morning of Day -1 through morning of Day 2), and the rest of study period consisted of 25 outpatient visits including the End-of-Study (EOS) visit.

Participants were randomised in a 1:1 ratio to receive a single SC injection of either RGB-14-X 60 mg (Treatment A; test product) or US-sourced Xgeva 60 mg (Treatment B; reference product) in the morning of Day 1 after an overnight fasting of at least 8 hours.

Additional study treatment: Calcium 1000 mg and Vitamin D3 800 IU daily from Day 1 to the end of the study.

Randomisation was stratified by a factor based on body mass index (BMI; 19 to 21.99 kg/m^2, 22 to 24.99 kg/m^2, 25 to 26.99 kg/m^2, 27 to 29 kg/m^2) on Day –1 to handle the possible effect of body weight (or BMI) on the PK of denosumab. The randomisation was also stratified for each site.

Figure 1: Study design



Abbreviations: SC: subcutaneous; PD: pharmacodynamic; PK: pharmacokinetic.

Study participants – Key eligibility criteria

Healthy male subjects between 28 and 55 years of age with a body weight ≥ 55 and ≤ 90 kg and a BMI between 19.0 and 29.0 kg/m^2 were eligible. The exclusion criteria were established to ensure the recruitment of a healthy population with no conditions that affect bone metabolism and no prior exposure to denosumab or any other drugs that treat osteoporosis or influence bone metabolism.

Objectives and Endpoints

The primary objective was to characterise and compare the PK of a single 60 mg SC dose of RGB-14-X with a single 60 mg SC dose of Xgeva in healthy adult male participants. Primary PK endpoints were maximum observed serum concentration (C_{max}), area under the concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration ($AUC_{0\text{-}last}$) and area under the concentration-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$). Secondary endpoints included additional PK parameters ($AUC_{0\text{-}119d}$, $AUC_{119d\text{-}last}$, t_{max}, $t_{1/2}$), the PD profile (%CfB in sCTx level, AUEC of %CfB in sCTx, I_{max} of sCTx), safety, tolerability and immunogenicity.

PK/PD/ADA sampling time points

Blood samples for PK analysis were collected at day 1 (pre-dose and 1h and 8h post-dose), day 2 (24h), 3, 4, 5, 6, 8, 10, 12, 14, 16, 21, 28, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 217 and 252 (or in case of early termination).

The PD blood sampling for determination of sCTx levels was to be performed between 7:30 a.m. and 10:00 a.m. after overnight fasting of at least 8 hours. Blood samples for PD analysis were collected at day 1 pre-dose, day 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 21, 28, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 217 and 252 (or in case of early termination).

Blood samples for immunogenicity assessments were collected at day 1 pre-dose, day 14, 28, 63, 91, 119, 147, 175, 217 and 252.

Sample size

In the case of a single 60 mg dose, an equivalence test of means using 2 one-sided tests on data from a parallel-group design with an evaluable sample size of 69 participants per arm achieves 90% power at a 5% significance level when the true difference between the means was 5%, and inter CV% was 35% for AUC, and the equivalence limits are 80% and 125% for the 90% confidence interval (CI) of the ratio of test and reference products, calculated based on analysis of variance (ANOVA) on logarithmic transformed data. Assuming a drop-out rate of 20% the total sample size planned was 172 participants (86 participants per arm). All statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Blinding

A double-blind design will be used to minimise any bias that may result from the Sponsor or staff being aware of the sequence assignment for an individual subject, e.g., assigning relationship of AEs to IMP, bioanalysis of PK samples, exclusion of bioanalytical data from the PK evaluation and determination of analysis populations. Consequently, during the study conduct, all subjects and site personnel (except for randomisation biostatistician, pharmacy staff [or unblinded clinical staff] and unblinded monitor) as well as subcontracted laboratory personnel will be blinded to the assigned study treatment. Since the IMP vials will not be blinded, the pharmacy staff (or unblinded clinical staff) and a monitor responsible for checking IMP accountability will be unblinded. The Sponsor including bioanalytical laboratory (PK and immunogenicity) and the Sponsor Medical Monitor will be blinded to assignment of study treatment throughout the conduct of the study.

Measures were in place to prevent unblinding of blinded site staff, including communication restrictions and separation of functions to handle the IMP and records indicating the treatment allocation of participants. These measures were detailed in the study specific Blinding Maintenance Plan.

Statistical methods

PK endpoints: Serum denosumab concentration data were listed and summarised (by nominal time and by treatment, treatment and BMI group, treatment and site) in tabular and graphical format. The PK parameters of RGB-14-X and US-Xgeva were calculated from individual serum concentration versus time profiles via non-compartmental analysis (NCA) using validated software (Phoenix WinNonlin version 8.3). PK parameter data for denosumab were also listed and summarised (by treatment, treatment and BMI group, treatment and site).

Assessment of PK biosimilarity: Two one-sided test (TOST) was used. The null hypothesis was that the test and reference were not biosimilar. The alternate hypothesis was that the test and reference were biosimilar. For each of the primary PK parameters (Cmax, AUC0-last, AUC0-inf) a linear mixed model ANOVA was used to test the significance of the effects of treatment. In this analysis, treatment and site were modelled as fixed factors, and BMI was examined in the model as continuous covariate. The PK parameters were natural log transformed prior to analysis. Point estimates and 90% CIs for the "test/reference" geometric mean ratios of these primary PK parameters were tabulated. Back transformation provided the ratio of geometric means and 90% CIs for these ratios. Equivalence of the primary endpoint was determined if 90% CI for the ratio of geometric mean of RGB-14-X to the US-sourced Xgeva was within the acceptance interval of 0.8 to 1.25.

PD endpoints: Serum CTx concentration data, including the sCTx change from baseline (CfB) (post-dose sCTx - baseline sCTx), and the %CfB (100 × CfB/baseline sCTx) were listed and summarised by nominal time and

treatment. The sCTx PD parameters were calculated from individual sCTx %CfB versus time profiles via NCA methods (drug effect model) using validated software (Phoenix WinNonlin version 8.3). PD parameters were listed and summarised by treatment.

Immunogenicity endpoints: The incidence of participants who developed binding anti-drug antibodies (ADAs) (i.e., ADA-positive) and neutralizing ADAs (NAb-positive) by visit and overall were to be compared descriptively between the treatment groups.

Safety endpoints: Continuous data were summarised by treatment group using descriptive statistics (n, mean, standard deviation (SD), minimum, median and maximum). Categorical data were summarised by treatment group and overall using frequency tables (number and percentage).

PK results

Participant flow

Of the 609 participants screened for the study, 165 participants were randomised (103 in Site1, 26 in Site2, and 36 in Site3). All randomised participants received the study drug, and 162 (98.2%) participants completed the study. Three (1.8%) participants discontinued from the study:

- One participant (RGB-14-X group) was withdrawn from the study due to physician decision and the EOS visit was on Day 28.
- One participant (RGB-14-X group) withdrew from the study for personal reasons. The EOS visit was on Day 148.
- One participant (US-sourced Xgeva) was withdrawn from the study due to other reason and the EOS visit was on Day 62.

There were no discontinuations from the study due to AEs.

All randomised participants were included in all analysis sets (RGB-14-X n=83; US-Xgeva n=82).

Protocol deviations

Most of the protocol deviations reported were minor (1840 minor deviations versus 74 major deviations). There were no critical protocol deviations.

A total of 43 (26.1%) participants in the Safety Population had major protocol deviations. The most common categories of major protocol deviation were "other" (15.8% participants) and deviations due to COVID-19/pandemic-related circumstances (7.9% participants). Most deviations in the other category were missed visits due to AE or other reasons, and therefore no assessments or blood sample collection was done; the remaining deviations in this category included discarding of a sample due to laboratory error, inability to enter details of concomitant medication into ClinBase and eCRF as diary pages were deemed to be missing, and EOS visit earlier to the scheduled date due to the inability of the participant to attend the visit on the scheduled date.

One participant had a major deviation related to inclusion/exclusion criteria. This was considered as deviation to Inclusion criterion no. 5. This deviation did not impact any population analysis sets.

Protocol deviations did not lead to exclusion of participants from safety, PK or PD, or immunogenicity analysis population. Protocol deviations did not lead to withdrawal of participants from study.

Table 3: Summary of Major Protocol Deviations (Safety Population)

	RGB-14-X 60 mg (N = 83)	US-sourced Xgeva® 60 mg (N = 82)	Overall (N = 165)
Protocol Deviation Category	**n (%) E**	**n (%) E**	**n (%) E**
Any major protocol deviation	20 (24.1) 34	23 (28.0) 40	43 (26.1) 74
Subject did not meet the inclusion/exclusion criteria	0	1 (1.2) 1	1 (0.6) 1
Subject did not comply with meals and dietary protocol restrictions as stated in Section 5.3.1 of the protocol	2 (2.4) 3	2 (2.4) 2	4 (2.4) 5
Time window deviations for safety measurements	1 (1.2) 1	5 (6.1) 8	6 (3.6) 9
Time window deviations for PD blood sampling	2 (2.4) 6	2 (2.4) 2	4 (2.4) 8
Other protocol deviations	15 (18.1) 19	11 (13.4) 15	26 (15.8) 34
Any protocol deviations due to COVID-19/Pandemic-related circumstances	4 (4.8) 5	9 (11.0) 12	13 (7.9) 17

N = number of subjects in Safety Population in specific treatment or overall; n = number of subjects in specific category in Safety Population in specific treatment or overall; E = number of major protocol deviations in specific category in Safety Population in specific treatment or overall; % = (n/N)*100.

Data sets analysed

All randomised participants were included in all analysis sets.

Demographic and baseline data, medical history and prior/concomitant medication

The study included male participants with a mean age (standard deviation, SD) of 39.4 (7.69) years. The majority of participants (77.6%) were of White race. Most participants (93.9%) were Not Hispanic or Latino by ethnicity. The demographic characteristics were generally well balanced between the test and reference treatment groups.

History of substance use, medical history, and prior and concomitant medication by participant are presented in Listing 16.2.4.2, Listing 16.2.4.3, and Listing 16.2.4.4, respectively.

Table 4: Demographic Characteristics by Treatment and Overall (Safety Population)

Variable/Category	RGB-14-X 60 mg (N = 83)	US-sourced Xgeva 60 mg (N = 82)	Overall (N = 165)
Age (Years)			
n	83	82	165
Mean	39.1	39.8	39.4
SD	7.81	7.59	7.69
Median	39.0	38.0	39.0
Minimum	28	27	27
Maximum	55	56	56
Sex, n (%)			
Male	83 (100)	82 (100)	165 (100)
Race, n (%) #			
American Indian or Alaska Native	0	1 (1.2)	1 (0.6)
Asian	2 (2.4)	2 (2.4)	4 (2.4)
Black or African American	2 (2.4)	6 (7.3)	8 (4.8)
Native Hawaiian or Other Pacific Islander	0	0	0
White	65 (78.3)	63 (76.8)	128 (77.6)
Not reported	1 (1.2)	0	1 (0.6)
Other	13 (15.7)	11 (13.4)	24 (14.5)
Ethnicity, n (%)			
Hispanic or Latino	7 (8.4)	2 (2.4)	9 (5.5)
Not Hispanic or Latino	75 (90.4)	80 (97.6)	155 (93.9)
Not reported	0	0	0
Unknown	1 (1.2)	0	1 (0.6)
Other	0	0	0
Height (cm)			
n	83	82	165
Mean	178.02	178.68	178.35
SD	6.829	6.855	6.829
Median	178.00	178.35	178.00
Minimum	156.0	165.0	156.0
Maximum	193.0	198.0	198.0
Weight (kg)			
n	83	82	165
Mean	78.17	78.96	78.56
SD	8.053	8.448	8.236
Median	78.10	80.60	79.30
Minimum	59.4	56.8	56.8
Maximum	89.8	90.4	90.4
BMI (kg/m^2)			
n	83	82	165
Mean	24.66	24.70	24.68
SD	2.139	2.129	2.127
Median	24.70	24.55	24.70
Minimum	19.4	20.1	19.4
Maximum	28.8	28.6	28.8

*N = number of subjects in Safety Population in specific treatment or overall; n = number of subjects in specific category in the Safety Population in specific treatment or overall; % = (n/N)*100.*
Height at screening, Weight, and BMI at Day -1 Visit were considered.
 # One subject reported 2 races.
Abbreviations: BMI = body mass index; SD = standard deviation; US = United States.

Primary PK analysis

Statistical analysis to assess biosimilarity of serum PK parameters of RGB-14-X and Xgeva (PK Population) including BMI as a covariate is presented in the table below. The geometric mean ratio (90% CI) was 1.029 (0.96, 1.10) for C_{max}, and 1.110 (1.04, 1.18) for both $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$. The geometric mean ratios and the corresponding 90% CIs of RGB-14-X versus US-sourced Xgeva for C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were within the equivalence range of 0.80 to 1.25, noting that the 90% CI for $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ geometric mean ratio had the lower bound close to 1 but excluding the value of 1. Similar results were obtained when BMI was not included as a covariate in the model.

Table 5: Statistical Analysis to Assess Biosimilarity of Serum PK Parameters of RGB-14-X and Xgeva (PK Population)

	Geometric Mean (95% CI)						
Parameter (unit)	**n**	**RGB-14-X 60 mg**	**n**	**US-sourced Xgeva® 60 mg**	**Geometric Mean Ratio (RGB-14-X/US-sourced Xgeva®)**	**90% CI**	**Inter CV%**
C_{max} (ng/mL)	83	5404.543 (5083.22, 5746.18)	82	5251.195 (4938.00, 5584.25)	1.029	0.96, 1.10	26.2
$AUC_{0\text{-last}}$ (day*ng/mL)	82	286695.501 (270536.63, 303819.52)	81	258324.233 (243709.01, 273815.93)	1.110	1.04, 1.18	24.6
$AUC_{0\text{-inf}}$ (day*ng/mL)	82	286734.377 (270567.94, 303866.75)	81	258382.880 (243759.47, 273883.56)	1.110	1.04, 1.18	24.6

n = number of subjects with a specific parameter for a treatment.

Abbreviations: ANOVA = analysis of variance; $AUC_{0\text{-inf}}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-last}}$ = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; BMI = body mass index; C_{max} = maximum observed serum concentration; CI = confidence interval; PK = pharmacokinetic; US =United States.

Linear mixed model ANOVA was used, with treatment and site as fixed factors and BMI as continuous covariate after log-transformation of PK parameter. The term "subject" was not included in the statistical model as random effect. This led to non-estimable least square means using the available analysis data. BMI was statistically significant in the analysis.

Serum Denosumab Concentration-time Data

Arithmetic mean denosumab serum concentrations are presented in linear scale (±SD) and semi-logarithmic scale for the PK Population by treatment in the figures below.

Following a single administration of denosumab 60 mg SC, there were no evident differences in t_{max} between RGB-14-X and US-sourced Xgeva treatment arms and t_{max} was consistent across BMI groups and sites. PK profiles shape was as expected for a drug with parallel linear and nonlinear PK due to the target-mediated pathway. Indeed, following t_{max}, a first slope can be observed (approximately down to serum concentrations of 100 ng/mL) corresponding to a phase where the target is saturated (thus linear PK prevails; slope #1), followed by a second slope (approximately down to 5 ng/mL) corresponding to a phase where the target is no longer saturated (thus linear and nonlinear elimination pathways work in parallel, slope #2), finally followed by a slope corresponding to a phase where drug concentrations are very low (slope #3). This last phase was not observed for all participants, even in cases when they completed the planned PK assessments. Indeed, for some participants the last phase might have occurred when concentrations fell below the lower limit of

quantification (LLOQ) (1 ng/mL for normal samples and 1.5 ng/mL for lipemic or haemolyzed samples). For other participants on the other hand, displaying overall higher concentrations, the last slower decay was likely not observed as the sampling period was not sufficient to achieve the required decrease in concentration values.

Serum concentrations were quantifiable up to 6024 hours post-dose (Day 252) in 31/81 participants for RGB-14-X and 21/81 for US-sourced Xgeva. Two participants in RGB-14-X group and 1 in US-sourced Xgeva group withdrew, thus their serum concentrations at 6024 hours were not available.

Average denosumab exposure decreased with increased BMI. No evident differences were noticed across sites for average denosumab exposure.

Figure 2: Arithmetic Mean (± SD) Pharmacokinetic Serum Concentration Data vs Nominal Time by Treatment (Linear Scale) (PK Population)

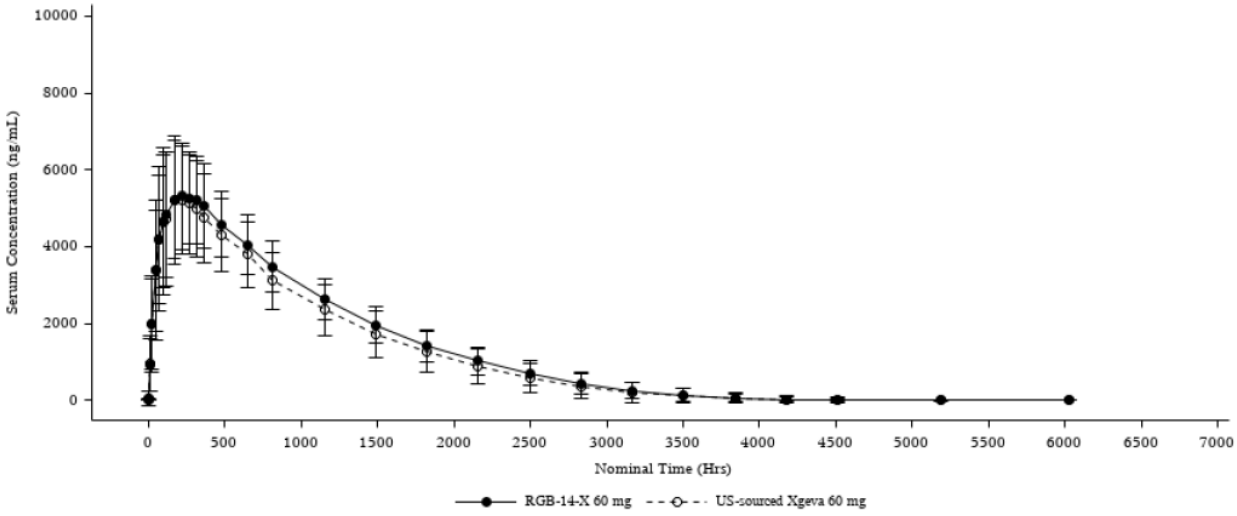
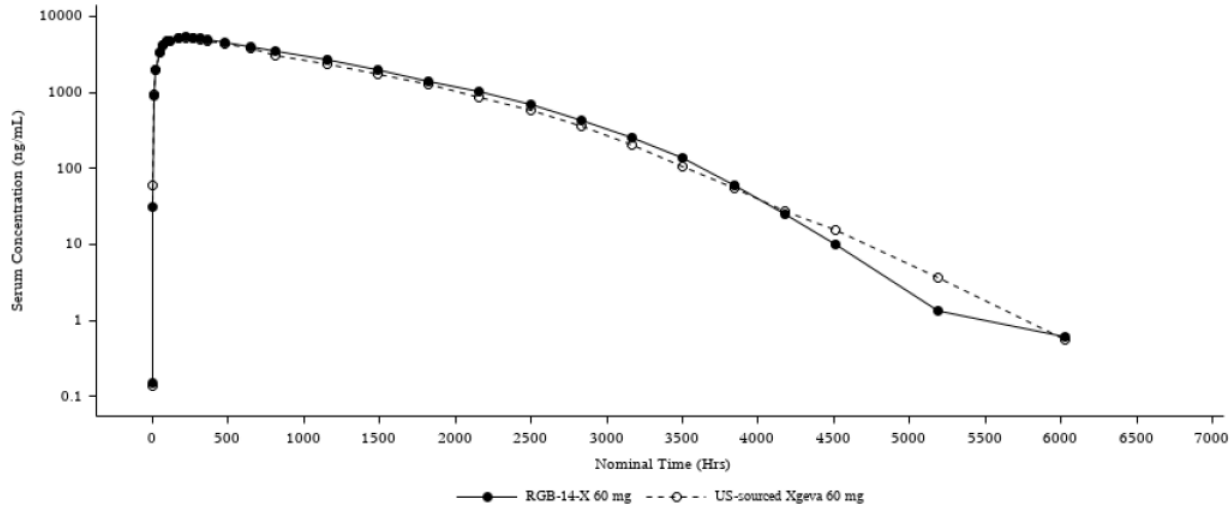


Figure 3: Arithmetic Mean Pharmacokinetic Serum Concentration Data vs Nominal Time by Treatment (Semi-Logarithmic Scale) (PK Population)



Pharmacokinetic Parameter Data

Key summary statistics of denosumab PK parameters are presented in the table below.

For 2 participants (1 in RGB-14-X group and 1 in US-sourced Xgeva group), $AUC_{119d\text{-}last}$ could not be calculated, while $AUC_{0\text{-}119d}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, and $t_{1/2}$ were calculated but excluded from further analysis due to early withdrawal from the study. This was justified by the fact that: (i) withdrawal happened before Day 119, and (ii) at the last planned visit with PK sampling (Day 21 and Day 49, respectively) and at the subsequent ET visits (approximately 648 hours and 1464 hours post-dose, respectively) denosumab concentrations were still in the order of 103 ng/mL. In addition, for the participant in the RGB-14-X group, the percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation ($\%AUC_{ex}$) was >20% and the λz interval span was <1.5-fold the corresponding $t_{1/2}$ estimate. A third participant (RGB-14-X group) withdrew from the study; however, the collected data were deemed to be sufficient to reliably determine $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, and $t_{1/2}$, which were thus flagged but retained for further analysis. Indeed, for this participant, at the last planned visit with PK sampling (Day 133), denosumab concentration was of the same order of magnitude of LLOQ, and the subsequent sample (at ET visit, approximately 360 hours later) was below the LLOQ. AUC0-inf and t1/2 were flagged (but retained for further analysis) for 2 other participants (1 in RGB-14-X group and 1 in US-sourced Xgeva group) due to adjusted coefficient of determination (R2 adj) < 0.9.

No evident difference was observed between RGB-14-X and US-sourced Xgeva in terms of C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$. Both RGB-14-X and US sourced Xgeva C_{max} was lower with increasing BMI, while only US-sourced Xgeva $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ appeared to decrease with BMI. Limited number of participants (n=8 to n=36) in certain BMI groups might explain this apparent difference in BMI-exposure relationship between RGB-14-X and US sourced Xgeva.

No trend was observed between denosumab serum PK parameters and site.

Table 6: Summary Statistics of Denosumab Serum PK Parameters by Treatment (PK Population)

Parameter (unit)	**Statistics**	**RGB-14-X 60 mg (N = 83)**	**US-sourced Xgeva 60 mg (N = 82)**
C_{max} (ng/mL)	n	83	82
	Geometric Mean	5,534.6	5,365.6
	Geometric CV%	26.3	30.3
$AUC_{0\text{-}last}$ (day*ng/mL)	n	82	81
	Geometric Mean	287,260	257,870
	Geometric CV%	23.5	28.7
$AUC_{0\text{-}inf}$ (day*ng/mL)	n	82	81
	Geometric Mean	287,300	257,920
	Geometric CV%	23.5	28.7
$AUC_{0\text{-}119d}$ (day*ng/mL)	n	82	81
	Geometric Mean	278,660	251,540
	Geometric CV%	22.0	26.7
$AUC_{119d\text{-}last}$ (day*ng/mL)	n	82	81
	Geometric Mean	5,429.0	3,277.2
	Geometric CV%	225.1	284.7
t_{max} (day)	n	83	82
	Median	10.931	8.972

Parameter (unit)	Statistics	RGB-14-X 60 mg (N = 83)	US-sourced Xgeva 60 mg (N = 82)
	Minimum	2.95	1.96
	Maximum	26.97	27.04
$t_{1/2}$ (day)	n	82	81
	Geometric Mean	6.0141	5.9863
	Geometric CV%	19.7	27.1

n: number of subjects with a specific parameter; N: The number of subjects included in the PK Population for each treatment; CV coefficient of variation
Abbreviations: $AUC_{0\text{-}119d}$ = area under the concentration-time curve from time 0 to Day 119; $AUC_{119d\text{-}last}$ = area under the concentration-time curve from Day 119 to the last quantifiable concentration; $AUC_{0\text{-}inf}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}last}$ = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max} = maximum observed serum concentration; CV = coefficient of variation; PK = pharmacokinetic; SD = standard deviation; $t_{1/2}$ = terminal elimination half-life; t_{max} = time corresponding to occurrence of Cmax; US = United States.

Pharmacokinetics in the target population

No PK analyses were predefined for this study.

The design and methods of study RGB-14-101 are presented in the Clinical section below.

PK sampling time points

Denosumab concentrations were measured in samples collected during treatment period 1 on day 1 (week 0), 15 (week 2), 30 (week 4), during treatment period 2 on day 1 (week 26 same samples as period 1 day 183), 15 (week 28), day 30 (week 30) and 183 (week 52) and during treatment period 3 on day 1 (week 52 same samples as period 2 day 183), 15 (week 54), day 30 (week 56) and day 183 (week 78).

PK results

Table 7: Study RGB-14-101: Denosumab serum concentrations versus time – Main Period (Full Analysis Set)

Week (Day)	Statistic (ng/mL)	Prolia	RGB-14-P
0 (0)	n	225	238
	Geometric mean	0.56	0.55
	95% LCL g.mean	0.52	0.53
	95% UCL g.mean	0.6	0.58
	min	0	0
	median	0	0
	max	53.94	5.06
2 (14)	n	225	236
	Geometric mean	5418.05	5384.95
	95% LCL g.mean	5145.31	4732.17
	95% UCL g.mean	5705.25	6127.79
	min	507.3	0
	median	5622.74	6053
	max	13334.61	12402.19
4 (30)	n	227	237
	Geometric mean	4278.37	4613.21
	95% LCL g.mean	4057.35	4228.13
	95% UCL g.mean	4511.44	5033.37
	min	112.18	0
	median	4402.14	4796.48
	max	9730.51	12760.44

Week (Day)	Statistic (ng/mL)	Prolia	RGB-14-P
26 (183)	n	219	227
	Geometric mean	3.71	5.83
	95% LCL g.mean	2.79	4.27
	95% UCL g.mean	4.94	7.96
	min	0	0
	median	1.68	3.13
	max	569.44	1648.32
28 (197)	n	206	218
	Geometric mean	5019.86	5531.68
	95% LCL g.mean	4389.87	5006.69
	95% UCL g.mean	5740.26	6111.72
	min	0	0
	median	5571.7	5934.37
	max	11481.88	12315.1
30 (211)	n	215	220
	Geometric mean	3912.6	4823.9
	95% LCL g.mean	3364.95	4586.26
	95% UCL g.mean	4549.37	5073.85
	min	0	346.22
	median	4466.6	4928.16
	max	10605.21	11244.01
52 (366)	n	208	225
	Geometric mean	4.65	6.47
	95% LCL g.mean	3.36	4.63
	95% UCL g.mean	6.44	9.05
	min	0	0
	median	1.94	2.96
	max	540.02	1862.16

Note: During geometric mean calculations, zero concentrations (measured as BLQ) are changed to 0.5 ng/ml (LLOQ/2).

Figure 4: Study RGB-14-101: Denosumab serum concentrations versus time – Main Period (Full Analysis Set)

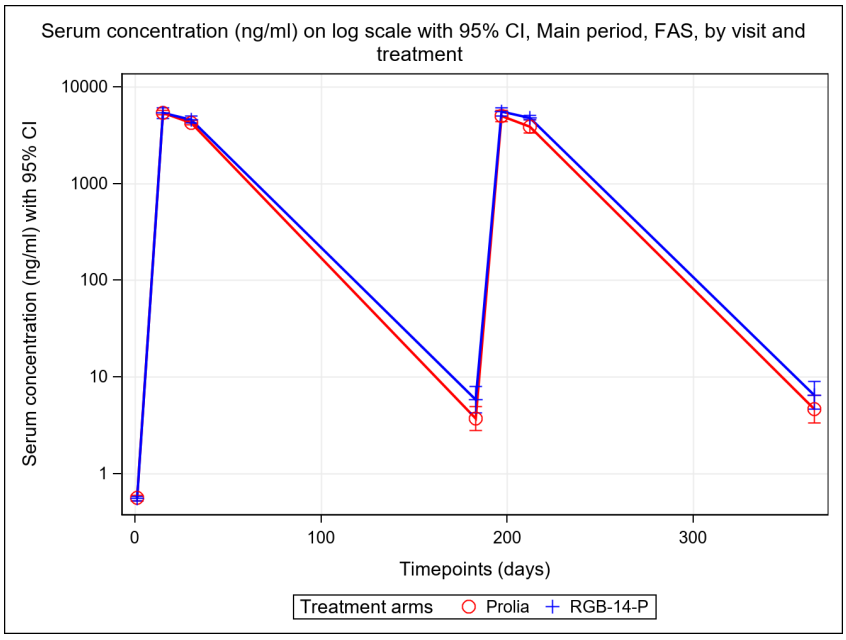
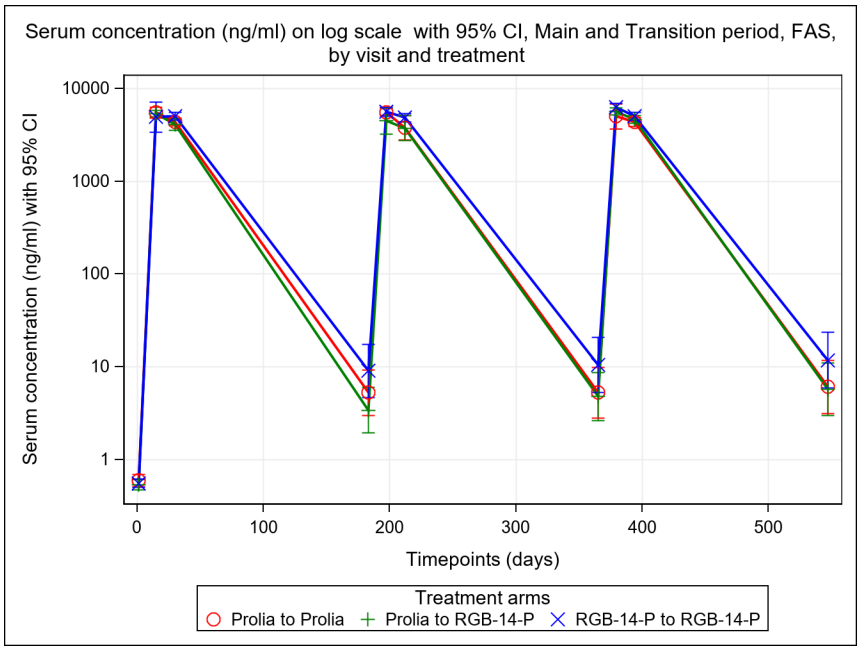


Table 8: Study RGB-14-101: Denosumab serum concentrations versus time – Transition Period (Full Analysis Set)

Week (Days)	Statistics (ng/ml)	Prolia to Prolia	Prolia to RGB-14-P	RGB-14-P to RGB-14-P
52 (366)	n	62	62	63
	Geometric mean	5.25	4.78	10.49
	95% LCL g.mean	2.79	2.63	5.25
	95% UCL g.mean	9.9	8.66	20.93
	min	0	0	0
	median	2.09	2.25	3.98
	max	511.68	433.09	1862.16
54 (380)	n	62	61	62
	Geometric mean	5012.22	5663.77	6293.85
	95% LCL g.mean	3669.22	5159.85	5728.1
	95% UCL g.mean	6846.8	6216.91	6915.46
	min	0	2607.29	2065.83
	median	6162.42	5795.86	6434.15
	max	11259.32	12825.27	13241.43
56 (394)	n	61	62	63
	Geometric mean	4383.05	4637.36	5041.58
	95% LCL g.mean	3917.78	4202.31	4587.62
	95% UCL g.mean	4903.57	5117.44	5540.46
	min	443.68	1320.03	2336.69
	median	4633.65	4821.93	5024.48
	max	8317.65	10025.89	12614.77
78 (546)	n	61	62	63
	Geometric mean	6.07	5.74	11.73
	95% LCL g.mean	3.14	2.98	5.87
	95% UCL g.mean	11.72	11.05	23.41
	min	0	0	0
	median	2.22	2.6	4.54
	max	822.69	574.7	2181.54

Note: During geometric mean calculations, zero concentrations (measured as BLQ) are changed to 0.5 ng/ml (LLOQ/2).

Figure 5: Study RGB-14-101: Denosumab serum concentrations versus time – Transition Period (Full Analysis Set)



2.5.2.2. Pharmacodynamics

Mechanism of action

Denosumab binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts. The binding of denosumab prevents RANKL from activating its receptor RANK on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumours with osseous metastases. Giant cell tumours of bone are characteris

ed by neoplastic stromal cells expressing RANK ligand and osteoclast-like giant cells expressing RANK receptor. Signalling through the RANK receptor contributes to osteolysis and tumour growth. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclast-like giant cells. In patients with giant cell tumour of bone, denosumab binds to RANKL, significantly reducing or eliminating osteoclast-like giant cells. Consequently, osteolysis is reduced and proliferative tumour stroma can be replaced with non-proliferative, differentiated, woven new bone which may show an increase in density.

Primary and secondary pharmacology

Study RGB-14-001

PD endpoints

- Percent change from baseline (%CfB) in serum carboxyl-terminal telopeptide of type I collagen (sCTx) level
- Area under the effect-time curve (AUEC) of %CfB in sCTx
- Maximum percent inhibition (I_{max}) of sCTx

PD sample collection

The PD blood sampling for determination of sCTx levels was to be performed between 7:30 a.m. and 10:00 a.m. after overnight fasting of at least 8 hours. Blood samples for PD analysis were collected at day 1 pre-dose, day 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 21, 28, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 217 and 252 (or in case of early termination).

Out of the planned 4455 PD samples, 4374 samples were collected, and results were reported for 4364 samples. Five samples were excluded from PD data analysis, as they were characterised by major deviations in fasting status prior to blood sampling and clock time of collection:

• US-sourced Xgeva group, Day 217 visit

• RGB-14-X group, Day 3 and Day 4 visits

• US-sourced Xgeva group, Day 217 visit

• RGB-14-X group, Day 3 visit

PD results

Following a single administration of the test and the reference product, sCTx concentrations declined rapidly after dosing and started to re-increase from around 3500 hours (approximately 146 days) post-dose for both RGB-14-X and US-sourced Xgeva groups. Based on combined individual %CfB data, sCTx can be decreased almost by 100%, and the rapidity of re-increase is variable: for some participants the sampling period was not sufficient to return to values close to 0%CfB, while for others the %CfB increased even above the baseline. No apparent differences were observed in the sCTx (concentration and %CfB) mean profiles when comparing RGB-14-X and US-sourced Xgeva.

Figure 6: Arithmetic Mean (±SD) sCTx Concentration Data vs Nominal Time by Treatment (Linear Scale) (PD Population)

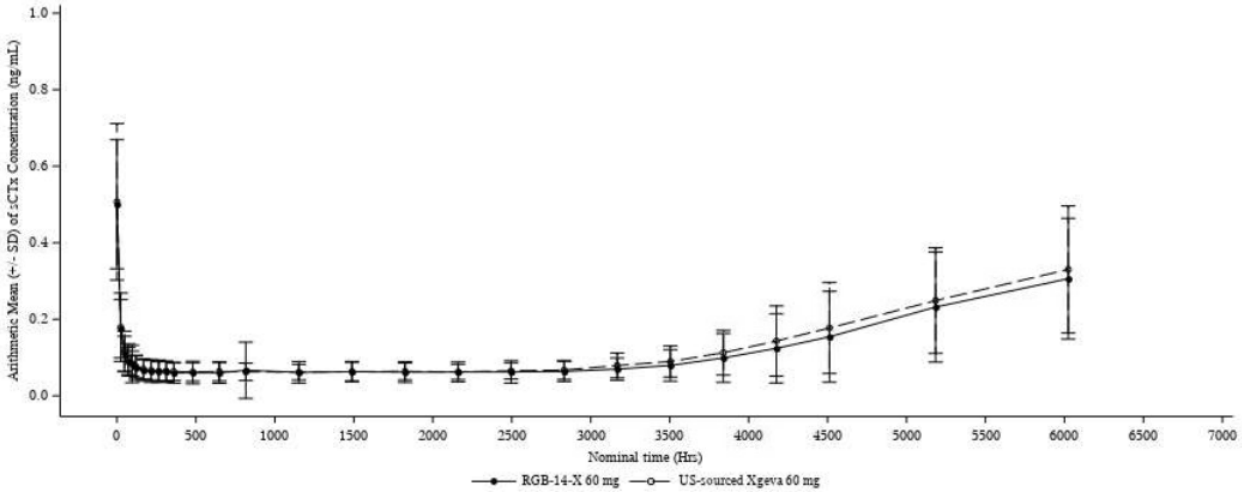
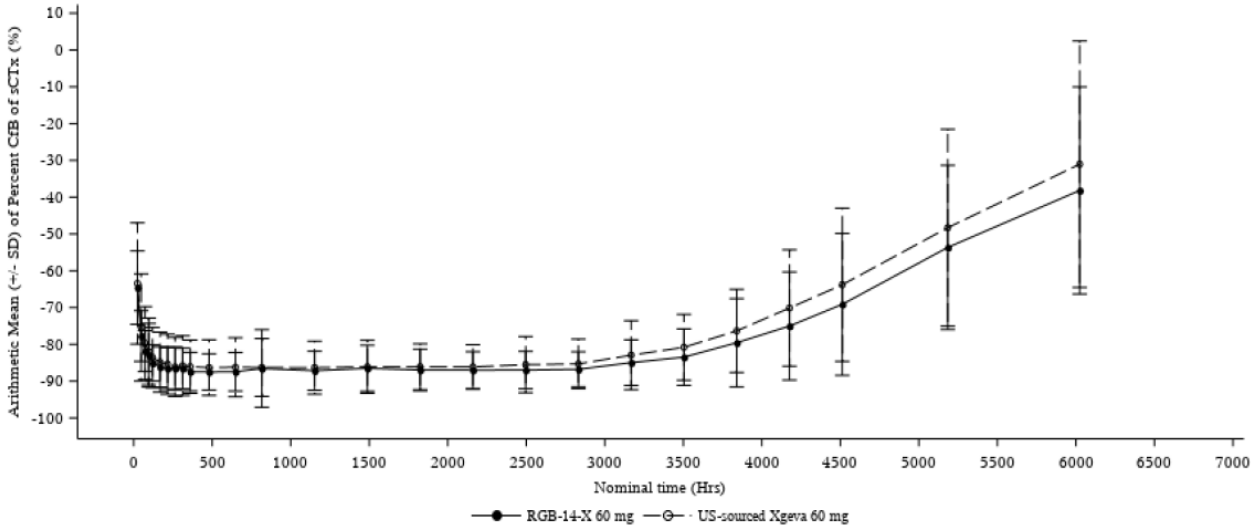


Figure 7: Arithmetic mean (±SD) sCTx %CfB data vs nominal time by treatment (Linear Scale)



Following single dose administration of denosumab 60 mg SC, geometric mean (gCV%) values for AUEC were 19196 day*% (10.4%) and 18388 day*% (14.6%), and for I_{max} were 90.226% (4.7%) and 89.345% (6.6%) for RGB-14-X and US-sourced Xgeva, respectively. Overall, PD parameter variability was low (gCV% < 15%). In the calculation of the sCTX area under the effect curve (AUEC) values, the area below the baseline was evaluated, the rebound areas (values above the baseline) were substituted with zero.

For 6 participants (4 in RGB-14-X group and 2 in US-sourced Xgeva group), AUEC was calculated but excluded from further analysis. Indeed, for these participants, sCTx sampling did not proceed up to Day 252 visit; as AUEC cannot be extrapolated and sCTx %CfB did not go back to zero by the time of the last sCTx sample, the AUEC parameter was considered to be partial.

No apparent difference was observed when comparing sCTx parameters between treatments (RGB-14-X or US-sourced Xgeva).

Table 9: Summary Statistics of PD (sCTx) Parameters by Treatment (PD Population)

Parameter (unit)	Statistics	RGB-14-X 60 mg (N = 83)	US-sourced Xgeva® 60 mg (N = 82)
AUEC (day*%)	n	79	80
	Geometric Mean	19196	18388
	Geometric CV%	10.4	14.6
I_{max} (%)	n	83	82
	Geometric Mean	90.226	89.345
	Geometric CV%	4.7	6.6

n: number of subjects with a specific parameter; N: The number of subjects included in the PD Population for each treatment.

As per the request, the AUEC values were recalculated in such a way that the rebound areas (as negative areas) were subtracted from the area below the baseline. The descriptive statistics of the AUEC parameter is shown in the table below. The table contains the results of both the original calculation and the recalculation. The difference in the mean or geometric mean AUEC values calculated by setting the rebound area to zero or subtracting it from the AUEC value is not more than 1%.

In addition, the table contains the number of subjects per treatment arm whose sCTx values crossed the baseline at any point during the study period. In the RGB-14-X arm 4 subjects' sCTx values, while in the Xgeva arm 14 subjects' sCTx values crossed the baseline. The low number of subjects whose sCTx values crossed the baseline (four for RGB-14-X arm and 14 for Xgeva arm) does not allow the statistical analysis of the rebound areas.

Taken together, the applicant's position is that the results of the additional calculations do not alter the original conclusions, i.e., no significant differences were observed in the sCTx AUEC parameter when comparing RGB-14-X and US-sourced Xgeva.

Table 10: Study RGB-14-001: Descriptive statistics of the sCTX AUEC parameter

		Rebound area subtracted[#] (recalculation)		**Rebound area set to zero (original calculation in CSR)**	
Parameter (unit)	**Statistics**	**RGB-14-X 60 mg (N=83)**	**US-sourced Xgeva 60 mg (N=82)**	**RGB-14-X 60 mg (N=83)**	**US-sourced Xgeva 60 mg (N=82)**
AUEC (day*%)	n	79	80	79	80
	n1	4	14	NA	NA
	Mean	19233	18446	19293	18565
	SD	2120.2	2690.3	1874.7	2396.6
	CV	11.0	14.6	9.7	12.9
	Geometric Mean	19089	18203	19196	18388
	Geometric CV	13.3	17.6	10.4	14.6
	Median	19585	18937	19585	18937
	Minimum	8157	7693	11790	9538
	Maximum	22567	22429	22570	22430

CV: coefficient of variation; n: number of subjects with a specific parameter; N: The number of subjects included in the pharmacodynamic population for each treatment; n1: number of subjects whose sCTx values crossed the baseline at any point during the study period. SD: standard deviation; sCTx: serum carboxyl-terminal telopeptide of type I collagen.
[#]The AUEC parameter is calculated as the area below 0% change in sCTx minus the area above 0% change.

RGB-14-101

PD endpoints

Primary PD endpoints:

- AUEC of %CfB sCTX0-m6 until Week 26

Secondary PD endpoints:

- %CfB in serum P1NP at Weeks 4, 26, 52, and 78
- %CfB in sCTX at Weeks 4, 26, 52, and 78

PD collection time points

CTX1 was measured in samples collected during treatment period 1 on days 1 (week 0), 8 (week 1), 15 (week 2), 30 (week 4), 60 (week 8), 90 (week 12), 120 (week 17) and 150 (week 21), during treatment period 2 on days 1 (week 26 same samples as period 1 day 183) and 183 (week 52) and during treatment period 3 on day 1 (week 52 same samples as period 2 day 183) and days 183 (week 78).

P1NP analysis was required for samples collected at the following time points: treatment period 1 day 1 (week 0, predose), treatment period 1 day 30 (week 4), treatment period 1 day 183/treatment period 2 day 1, treatment period 2 day 183/treatment period 3 day 1, treatment period 3 day 183.

PD set

Of the 473 enrolled and doses patients, 470 patients were included in the pharmacodynamic analysis set (PDS). A total of 3 participants had major deviations that led to exclusion from the PDS (RGB-14-P: 1 participant and Prolia: 2 participants), which were all related to procedures and tests.

PD results

Primary PD endpoint: AUEC of Percent Change from Baseline in sCTX (0-m6) Concentration Until Week 26

The analysis of the AUEC of %CfB in sCTX(0-m6) concentration for the PDS for the Main Period is presented in the table below.

The ratio of the geometric means of the AUEC of %CfB in sCTX concentration between the RGB-14-P and Prolia treatment groups was 1.01 (95% CI [0.978, 1.046]) and the difference between treatment groups was not statistically significant (p=0.494). Pharmacodynamic equivalence was concluded as the 95% CI of the treatment GMR was contained within the 80% to 125% equivalence margin.

Table 11: Analysis of sCTX %CfB AUEC $_{(0\text{-}m6)}$ (Pharmacodynamic Analysis Set for Main Period)

		Comparison between Study Treatment Groups	
Study Treatment	**Geometric Mean (95% CI)**	**Geometric Mean Ratio (95% CI)**	**P-value**
RGB-14-P (N=241)	13501.30 (12737.814, 14264.794)	1.01 (0.978, 1.046)	0.494
Prolia (N=229)	13344.65 (12583.291, 14106.002)		

The analysis was performed with a mixed-effects model ANCOVA on natural log transformed AUEC data as the dependent variable and the following model covariates: treatment arm, stratification factors (previous use of bisphosphonates [yes/no] and geographical region [Europe, US]), log of baseline sCTX.
In this presentation of results, log-scale fitted mean and treatment group differences (RGB-14-P - Prolia), together with associated 95% CIs were back-transformed. Delta method was applied to back transform geometric mean standard error used for the computation of corresponding 95% CIs.
In some instances, results were received with two test codes for sCTX (received as ZCTXG and ZCTX1); in these instances, based on instructions received from laboratory, the results received under code ZCTXG was considered as latest and used in this table.

The supplementary analysis (performed post-unblinding due to encountering data not planned during the study) the AUEC of %CfB in sCTX(0-m6) concentration for the PDS for the Main Period support the robustness of the primary analysis.

Table 12: Supplementary analysis of sCTX %CfB AUEC (0-6months) (Pharmacodynamic Analysis Set for Main Period)

		Comparison between Study Treatment Groups	
Study Treatment	**Geometric Mean (95% CI)**	**Estimated difference (95% CI)**	**P-value**
RGB-14-P (N=241)	11345.14 (9710.171 , 12980.118)	455.53 (-538.170 , 1449.228)	0.368
Prolia (N=229)	10889.62 (9247.934 , 12531.298)		

The analysis was performed with a mixed-effects model ANCOVA on AUEC data as the dependent variable and the following model covariates: Treatment Arm, Stratification factors (Previous use of bisphosphonates [yes/no] and Geographical region [Europe, US], baseline sCTX.
In some instances, results were received with two test codes for sCTX (received as ZCTXG and ZCTX1); in these instances, based on instructions received from laboratory, the results received under code ZCTXG was considered as latest and used in this table.

Percent Change from Baseline in Serum P1NP at Weeks 4, 26, 52 and 78

The mean %CfB in P1NP concentration was comparable between the RGB-14-P and Prolia treatment groups up to Week 52. The %CfB in P1NP shows the expected suppression that is maintained in the Transition Period. Switching Prolia to RGB-14-P did not impact the serum levels of P1NP, treatment response was maintained across all treatment arms at Week 78.

Table 13: Summary of P1NP Results by Visit - Main Period (Pharmacodynamic Analysis Set for Main Period)

Nominal Time Point	Statistic	RGB-14-P (N = 241)	Prolia (N = 229)	Overall Study (N = 470)
Predose Baseline				
Result	n (%)	240 (99.6)	228 (99.6)	468 (99.6)
	Mean	60.85	61.36	61.10
	SD	22.705	23.849	23.246
	Median	59.30	59.80	59.40
	Minimum	13.9	12.0	12.0
	Maximum	156.0	159.0	159.0
TP1 Day 30 - Week 4				
Result	n (%)	235 (97.5)	221 (96.5)	456 (97.0)
	Mean	46.96	47.68	47.31
	SD	18.680	17.221	17.971
	Median	44.70	47.20	45.45
	Minimum	12.0	12.0	12.0
	Maximum	112.0	109.0	112.0
TP1 Day 30 - Week 4				
CfB	n (%)	234 (97.1)	220 (96.1)	454 (96.6)
	Mean	14.02	13.75	13.89
	SD	11.027	11.807	11.400
	Median	12.90	12.95	12.90
	Minimum	-13.9	-22.2	-22.2
	Maximum	56.6	65.4	65.4
%CfB	n (%)	234 (97.1)	220 (96.1)	454 (96.6)
	Mean	22.10	20.22	21.19
	SD	14.905	15.091	15.008
	Median	23.53	21.52	22.09
	Minimum	-28.8	-36.8	-36.8
	Maximum	76.6	57.3	76.6
TP2 Day 1 - Week 26				
Result	n (%)	217 (90.0)	212 (92.6)	429 (91.3)
	Mean	18.94	19.49	19.21
	SD	11.671	9.486	10.639
	Median	16.60	17.00	16.90
	Minimum	12.0	12.0	12.0
	Maximum	166.0	83.9	166.0
CfB	n (%)	216 (89.6)	211 (92.1)	427 (90.9)
	Mean	41.83	42.04	41.93
	SD	22.557	23.298	22.899
	Median	40.95	41.30	41.00
	Minimum	-75.3	-51.9	-75.3
	Maximum	139.6	143.0	143.0
TP2 Day 1 - Week 26				
%CfB	n (%)	216 (89.6)	211 (92.1)	427 (90.9)
	Mean	65.92	62.89	64.42
	SD	17.828	29.294	24.202
	Median	70.16	68.72	69.00
	Minimum	-83.0	-243.7	-243.7

	Maximum	89.5	89.9	89.9
TP2 Day 183 - Week 52				
Result	n (%)	205 (85.1)	199 (86.9)	404 (86.0)
	Mean	19.62	19.56	19.59
	SD	10.297	8.965	9.652
	Median	17.20	17.50	17.35
	Minimum	12.0	12.0	12.0
	Maximum	118.0	87.4	118.0
TP2 Day 183 - Week 52				
CfB	n (%)	204 (84.6)	199 (86.9)	403 (85.7)
	Mean	42.77	42.91	42.84
	SD	23.344	22.571	22.937
	Median	41.20	41.90	41.80
	Minimum	-27.3	-9.8	-27.3
	Maximum	139.2	145.2	145.2
%CfB	n (%)	204 (84.6)	199 (86.9)	403 (85.7)
	Mean	65.04	64.14	64.60
	SD	19.131	21.591	20.363
	Median	70.29	70.16	70.27
	Minimum	-53.8	-61.7	-61.7
	Maximum	89.2	91.3	91.3

In this table, BLQ values were imputed as the LLOQ itself.
In some instances, results were received with two test codes for P1NP (received as ZP1NG and ZP1NB); in these instances, based on instructions received from laboratory, the results received under code ZP1NG was considered as latest and used in this table.

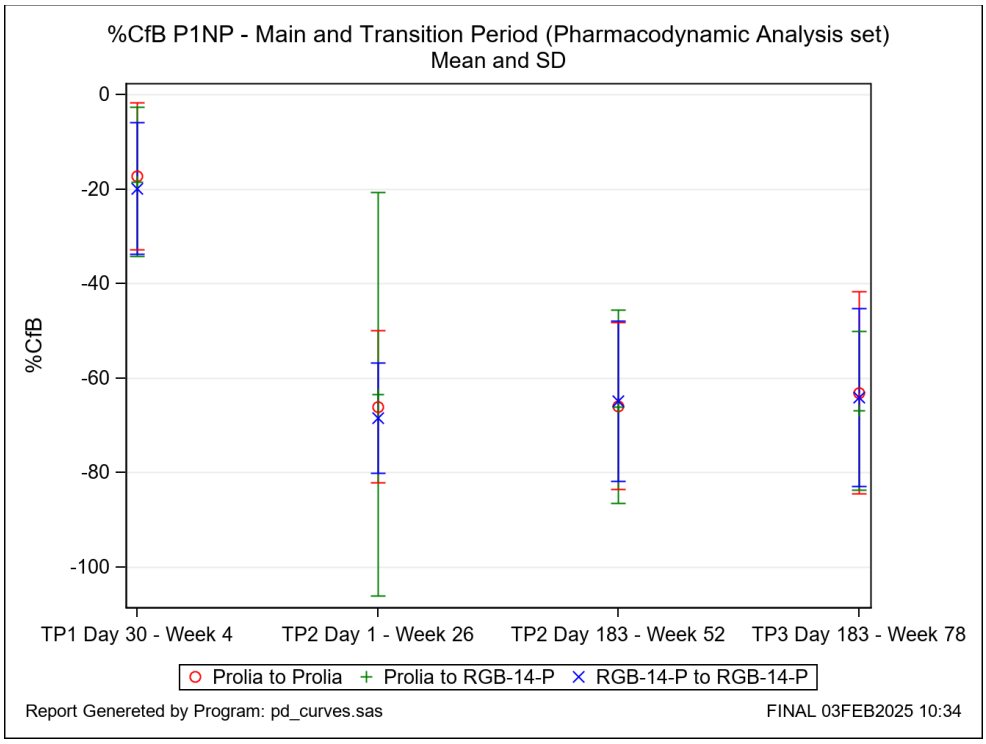
Table 14: Summary of %CfB in serum P1NP at Week 78 – Transition Period (Pharmacodynamics Analysis Set)

	Statistic	RGB-14-P to RGB-14-P (N = 60)	Prolia to RGB-14-P (N = 61)	Prolia to Prolia (N = 63)	Overall Study (N = 184)
TP1 Day 30 - Week 4					
%CfB	n (%)	60 (100)	59 (96.7)	62 (98.4)	181 (98.4)
	Mean	19.85	18.45	17.31	18.52
	SD	13.939	15.835	15.524	15.075
	Median	21.38	19.26	19.76	19.79
	Minimum	-22.3	-36.8	-29.6	-36.8
	Maximum	43.8	53.3	42.4	53.3
TP2 Day 1 - Week 26					
%CfB	n (%)	57 (95.0)	59 (96.7)	60 (95.2)	176 (95.7)
	Mean	68.42	63.41	66.08	65.94
	SD	11.693	42.677	16.098	27.183
	Median	70.20	70.78	69.17	70.07
	Minimum	31.3	-243.7	25.2	-243.7
	Maximum	89.5	88.0	86.0	89.5
TP2 Day 183 - Week 52					
%CfB	n (%)	60 (100)	60 (98.4)	61 (96.8)	181 (98.4)
	Mean	64.86	66.05	65.89	65.60
	SD	16.902	20.428	17.651	18.291
	Median	68.81	70.72	70.74	70.30
	Minimum	16.2	-46.0	2.5	-46.0
	Maximum	89.2	89.3	85.5	89.3
TP3 Day 183 - Week 78					
%CfB	n (%)	54 (90.0)	59 (96.7)	58 (92.1)	171 (92.9)
	Mean	64.12	66.91	63.08	64.73
	SD	18.845	16.816	21.364	19.051
	Median	70.57	71.58	69.42	70.34

	Statistic	RGB-14-P to RGB-14-P (N = 60)	Prolia to RGB-14-P (N = 61)	Prolia to Prolia (N = 63)	Overall Study (N = 184)
	Minimum	10.9	-13.1	-12.1	-13.1
	Maximum	87.1	89.3	86.7	89.3

*CfB: Change from Baseline, as reduction from baseline. %CfB: [(baseline - value)/baseline] *100. SD: standard deviation. N: The number of subjects included in the analysis set for each treatment and overall.*

Figure 8: Summary of %CfB in serum P1NP at Week 78 – Transition Period, (Pharmacodynamics Analysis Set)



Percent Change from Baseline in sCTX at Weeks 4, 26, 52 and 78

The median %CfB in the sCTX concentrations decreased at Weeks 4, 26, and 52. The median %CfB in the sCTX concentration was comparable between the RGB-14-P and Prolia treatment groups at Weeks 4, 26, and 52. The %CfB in sCTx shows the expected suppression that is maintained in the Transition Period. Switching RGB-14-P to Prolia did not impact the serum levels of sCTx, treatment response was maintained across all treatment arms at Week 78.

Table 15: Percentage Change from Baseline of sCTX Results at Week 4, 26 and 52 - Main period (Pharmacodynamic Analysis Set for Main Period)

Nominal Time Point	Statistic	RGB-14-P (N = 241)	Prolia (N = 229)	Overall Study (N = 470)
Predose Baseline				
Result	n (%)	240 (99.6)	228 (99.6)	468 (99.6)
	Mean	0.5118	0.5055	0.5087
	SD	0.2189	0.2183	0.2184
	Median	0.4860	0.4905	0.4870
	Minimum	0.099	0.056	0.056
	Maximum	1.240	1.290	1.290
TP1 Day 30 - Week 4				
Result	n (%)	235 (97.5)	221 (96.5)	456 (97.0)
	Mean	0.0576	0.0564	0.0570
	SD	0.0178	0.0160	0.0170
	Median	0.0490	0.0490	0.0490
	Minimum	0.049	0.049	0.049
	Maximum	0.190	0.142	0.190
%CfB	n (%)	234 (97.1)	220 (96.1)	454 (96.6)
	Mean	85.87	85.38	85.63
	SD	9.567	15.501	12.779
	Median	88.89	88.98	88.90
	Minimum	40.6	-83.9	-83.9
	Maximum	95.7	96.2	96.2
TP2 Day 1 - Week 26				
Result	n (%)	217 (90.0)	212 (92.6)	429 (91.3)
	Mean	0.1326	0.1474	0.1399
	SD	0.0894	0.1165	0.1038
	Median	0.1130	0.1175	0.1150
	Minimum	0.049	0.049	0.049
	Maximum	0.597	0.887	0.887
%CfB	n (%)	216 (89.6)	211 (92.1)	427 (90.9)
	Mean	69.74	61.51	65.67
	SD	23.212	83.764	61.218
	Median	75.95	75.47	75.81
	Minimum	-45.4	-1057.1	-1057.1
	Maximum	94.3	93.0	94.3
TP2 Day 183 - Week 52				
Result	n (%)	205 (85.1)	199 (86.9)	404 (86.0)
	Mean	0.1706	0.1693	0.1700
	SD	0.1414	0.1210	0.1316
	Median	0.1330	0.1430	0.1380
	Minimum	0.049	0.049	0.049
	Maximum	0.851	0.658	0.851
%CfB	n (%)	204 (84.6)	199 (86.9)	403 (85.7)
	Mean	62.90	58.84	60.89
	SD	28.995	63.566	49.182
	Median	70.49	70.90	70.87
	Minimum	-41.7	-651.8	-651.8
	Maximum	93.3	93.0	93.3

In this table, BLQ values were imputed as the LLOQ itself.
In some instances, results were received with two test codes for sCTX (received as ZCTXG and ZCTX1); in these instances, based on instructions received from laboratory, the results received under code ZCTXG was considered as latest and used in this table.

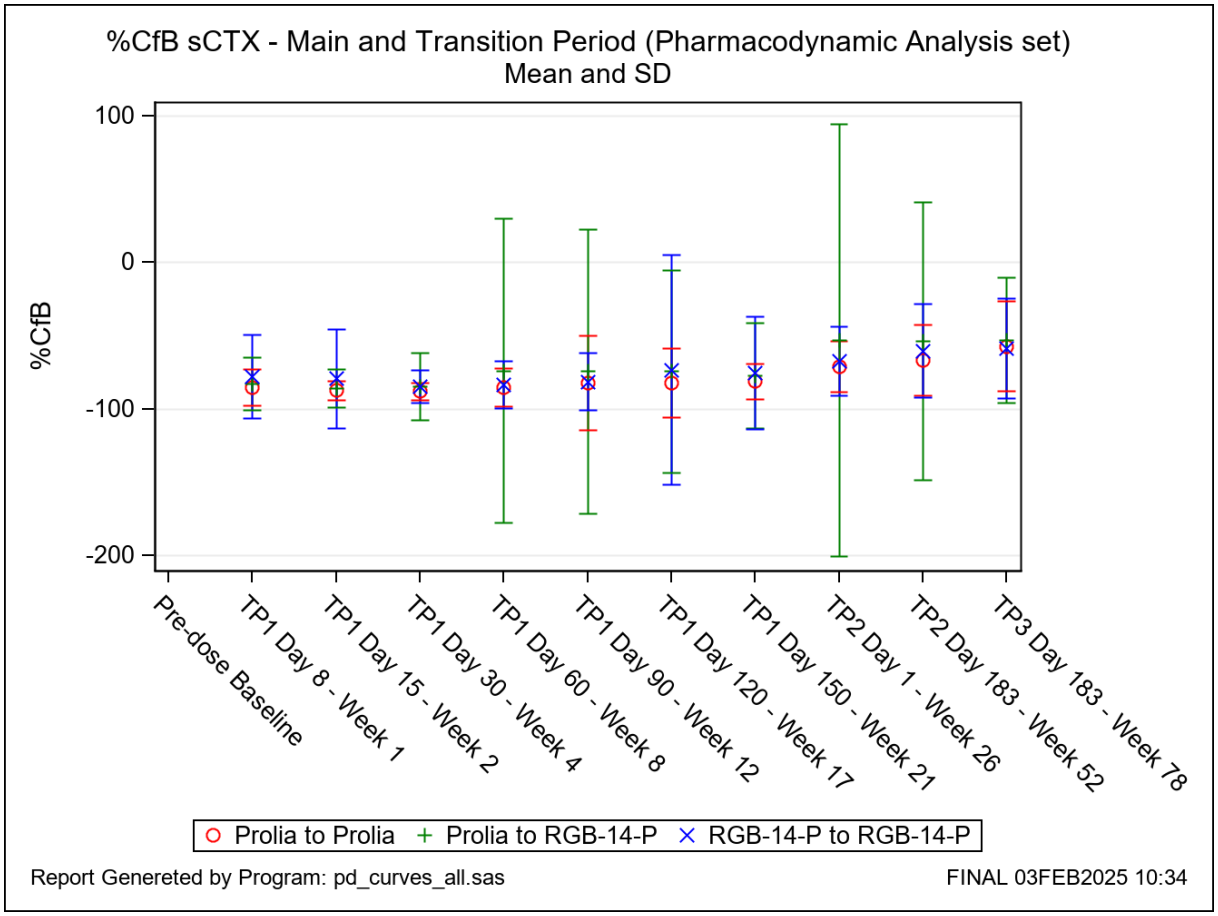
Table 16: Summary of %CfB in sCTX – Transition Period (Pharmacodynamics Analysis Set)

	Statistic	RGB-14-P to RGB-14-P (N = 60)	Prolia to RGB-14-P (N = 61)	Prolia to Prolia (N = 63)	Overall Study (N = 184)
TP1 Day 8 - Week 1					
%CfB	n (%)	60 (100)	59 (96.7)	62 (98.4)	181 (98.4)
	Mean	78.06	82.95	85.46	82.19
	SD	28.494	17.904	12.391	20.761
	Median	87.67	87.66	87.41	87.63
	Minimum	-81.5	-8.9	1.6	-81.5
	Maximum	94.5	93.0	94.9	94.9
TP1 Day 15 - Week 2					
%CfB	n (%)	60 (100)	58 (95.1)	62 (98.4)	180 (97.8)
	Mean	79.26	85.87	87.46	84.22
	SD	33.853	13.046	6.554	21.432
	Median	88.03	88.75	89.86	88.82
	Minimum	-149.2	-1.8	61.1	-149.2
	Maximum	94.9	94.8	94.9	94.9
TP1 Day 30 - Week 4					
%CfB	n (%)	60 (100)	59 (96.7)	62 (98.4)	181 (98.4)
	Mean	84.96	84.71	88.08	85.95
	SD	11.206	23.071	5.832	15.053
	Median	88.45	89.06	89.79	89.37
	Minimum	40.6	-83.9	64.7	-83.9
	Maximum	94.9	95.5	96.2	96.2
TP1 Day 60 - Week 8					
%CfB	n (%)	59 (98.3)	61 (100)	61 (96.8)	181 (98.4)
	Mean	83.42	74.02	85.41	80.92
	SD	16.093	103.930	13.069	61.367
	Median	87.93	88.31	89.33	88.31
	Minimum	-14.0	-723.2	20.4	-723.2
	Maximum	95.0	95.5	96.2	96.2
TP1 Day 90 - Week 12					
%CfB	n (%)	59 (98.3)	59 (96.7)	63 (100)	181 (98.4)
	Mean	81.47	74.52	82.43	79.54
	SD	19.553	96.825	32.389	59.311
	Median	87.17	88.00	88.89	88.00
	Minimum	-15.4	-655.4	-157.8	-655.4
	Maximum	95.1	95.2	94.9	95.2
TP1 Day 120 - Week 17					
%CfB	n (%)	60 (100)	61 (100)	62 (98.4)	183 (99.5)
	Mean	73.35	74.49	82.28	76.75
	SD	78.525	69.128	23.646	61.463
	Median	86.51	86.75	88.06	87.14
	Minimum	-520.3	-446.4	-65.0	-520.3
	Maximum	95.1	93.3	93.6	95.1
TP1 Day 150 - Week 21					
%CfB	n (%)	59 (98.3)	61 (100)	60 (95.2)	180 (97.8)
	Mean	75.50	77.22	81.24	78.00
	SD	38.603	35.755	12.190	31.083
	Median	84.56	83.56	85.37	84.60
	Minimum	-197.2	-187.5	40.0	-197.2
	Maximum	94.5	93.0	94.2	94.5
TP2 Day 1 - Week 26					
%CfB	n (%)	57 (95.0)	59 (96.7)	60 (95.2)	176 (95.7)
	Mean	67.29	53.23	71.27	63.93
	SD	23.572	147.679	17.483	87.004
	Median	75.00	75.54	78.11	75.50

	Statistic	RGB-14-P to RGB-14-P (N = 60)	Prolia to RGB-14-P (N = 61)	Prolia to Prolia (N = 63)	Overall Study (N = 184)
	Minimum	-16.7	-1057.1	24.4	-1057.1
	Maximum	94.3	93.0	93.0	94.3
TP2 Day 183 - Week 52					
%CfB	n (%)	60 (100)	60 (98.4)	61 (96.8)	181 (98.4)
	Mean	60.41	53.89	66.79	60.40
	SD	31.958	94.853	24.151	59.213
	Median	68.50	69.44	72.13	70.87
	Minimum	-30.1	-651.8	-58.6	-651.8
	Maximum	92.6	93.0	93.0	93.0
TP3 Day 183 - Week 78					
%CfB	n (%)	54 (90.0)	59 (96.7)	59 (93.7)	172 (93.5)
	Mean	58.70	53.32	57.38	56.40
	SD	34.117	42.855	30.562	36.135
	Median	72.32	64.78	63.43	66.24
	Minimum	-56.6	-191.1	-82.4	-191.1
	Maximum	93.3	88.8	93.0	93.3

*%CfB: [(baseline - value)/baseline] *100. SD: standard deviation. N: The number of subjects included in the analysis set for each treatment and overall.*

Figure 9: Summary in %CfB in sCTX – Transition Period (Pharmacodynamics Analysis Set)



2.5.3. Discussion on clinical pharmacology

PK equivalence data for RGB-14-X were generated in a single PK study in healthy volunteers (RGB-14-001) following a single SC injection compared to US-approved Xgeva. In addition, a Phase 3 confirmatory study in female patients with postmenopausal osteoporosis (RGB-14-101) evaluated PD characteristics following multiple SC administrations of RGB-P and US-approved Prolia.

Bioanalytical methods

The presented assay for determination of denosumab concentrations in human serum of healthy volunteers and patients with postmenopausal osteoporosis was well described and met the ICH M10 acceptance criteria. Consequently, it is deemed fit-for-purpose and fully acceptable for its intended use in quantitative analysis of denosumab in human serum samples.

While the same commercial sCTX1 kit was employed for both studies, the analyses and validations were conducted by two separate laboratories, resulting in two distinct bioanalytical reports (Method 4 and Method 6). Cross-validation is not required, as data were not combined across studies. Overall, the sCTX was deemed fit-for-purpose and fully acceptable for its intended use. Regarding the commercial kit for P1NP determination, it has been adequately validated and is deemed suitable for its intended use. While some uncertainty persists due to the lack of selectivity data in serum of patients with postmenopausal osteoporosis, the acceptable parallelism data from study samples supports the assay's validity in the target population. This issue is not pursued further.

A standard three-step approach was used to detect and characterise ADA in accordance with the Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev.1) and on Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010): Screening of ADA-positive samples, confirmation of ADA-positivity and assessment of ADA titer in confirmed ADA-positive samples. Overall, the ADA and NAb assay were sufficiently validated for sensitivity, cut points, selectivity, intra- and inter-run precision, hook effect and stability, and are considered suitable for their intended use.

Pharmacokinetics in healthy volunteers (RGB-14-001)

Design and conduct of clinical study

The pivotal PK study RGB-14-001 was a Phase 1, double-blind, randomised, single dose, multi-center, 2-arm, and parallel-group study to establish PK equivalence between RGB-14-X and US-Xgeva in healthy male subjects. Eligible subjects were randomised in a 1:1 ratio to receive a single SC dose of 60 mg on Day 1 and followed up until Day 252.

According to the EMA "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010), a single-dose study in healthy volunteers with a low or the lowest therapeutic dose used in patients is usually the preferred design for bioequivalence studies. A parallel group design is acceptable given the expected long half-life of the monoclonal antibody. Since the reference product is only approved for SC administration, the SC route is considered acceptable.

The selected 60 mg SC dose is the established therapeutic dose for Prolia and lies near the dose-response plateau of denosumab. Since denosumab is eliminated via a non-target-mediated, linear pathway at higher concentrations and a target-mediated, non-linear pathway at lower concentrations, a lower dose would have increased sensitivity to PK differences, particularly in target-mediated elimination, and to PD variations. This

was also noted in the EMA SAs, where a sub-therapeutic dose was recommended. Consequently, selecting the 60 mg dose limits the study's ability to detect these potential differences, particularly for target-mediated elimination. This limitation is acknowledged but not further investigated. The use of only the US-reference product for the clinical study is considered acceptable, as comparability based on physico-chemical and in vitro functional characterization has been demonstrated between RGB-14-X, the EU-sourced reference product, and the US-sourced comparator product.

The batches used for this study were documented for both products, including details on protein concentration, mean extractable volume, and maximum extractable dose. The doses relative to the label claim were found to be within an acceptable range for both RGB-14-X and Xgeva-US, at 99.2% and 98.2% respectively.

Study objectives and endpoints were appropriate for a pivotal biosimilar PK study. The primary objective was to establish PK equivalence between RGB-14-X and US-Xgeva after a single 60 mg SC injection in healthy male subjects. The co-primary endpoints of $AUC_{0\text{-inf}}$ and C_{max} were selected following EMA/CHMP/BMWP/403543/2010 and was supported in both EMA Scientific Advices. $AUC_{0\text{-last}}$ has been designated as a co-primary endpoint as well and is principally considered acceptable, even though it is not explicitly required to be a primary endpoint according to EMA guidance. A conservative bioequivalence approach was used based on the GLSM ratios of the primary PK parameters. In accordance with EMA guidance, bioequivalence was concluded if the ratio of GLSM and corresponding 90% CI are contained within the predefined bioequivalence range of 0.80 to 1.25. Secondary PK objectives included additional PK parameters. The selected PK sampling days allowed adequate coverage of the expected time of C_{max} and the elimination phase.

Overall, the study design was acceptable and in line with relevant EMA guidance (EMA/CHMP/BMWP/403543/2010) and previous EMA scientific advice (EMA/CHMP/SAWP/338801/2019, EMA/CHMP/SAWP/260988/2020).

Healthy male subjects between 28 and 55 years of age with a body weight ≥ 55 and ≤ 90 kg and a BMI between 19.0 and 29.0 kg/m^2 were eligible. Stratification by BMI (19 to 21.99 kg/m^2, 22 to 24.99 kg/m^2, 25 to 26.99 kg/m^2, 27 to 29 kg/m^2) and study site is supported. Participants must have taken calcium and Vitamin D3 daily as concomitant medication starting from Day 1 until EOS. This is acceptable, since supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients, according to the SmPC of Xgeva. Baseline characteristics were overall balanced between the groups. The mean age of study participants was 39.4 years, the mean body weight was 78.56 kg and the mean BMI 24.68 kg/m^2. Three subjects were marginally outside the acceptable age or weight ranges, however this is not expected to have a clinically meaningful impact on the results of the study.

Due to the expiry of the Xgeva batch, the applicant decided to stop enrolment early after 165 participants instead of the planned number of 172 subjects. These 165 participants were randomised and dosed (RGB-14-X n=83, US-Xgeva n=82) of which 162/165 (98.2%) participants completed the study. Three (1.8%) participants discontinued early from the study due to participant withdrawal (for personal reasons), physician decision and other. All randomised participants were included in all analysis sets. No issues arise from these data.

Pharmacokinetic results

The serum concentration-time curves of RGB-14-X and of US-Xgeva showed considerable overlap, with both substances reaching maximum serum concentrations (t_{max}) at comparable time points and declined in similar pattern.

PK assessments demonstrated that the geometric means of the co-primary endpoints C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}last}$ were comparable between treatment arms and the primary statistical analysis demonstrated that the 90% CIs of GLSM ratios were well contained within the acceptable bioequivalence range (0.80 – 1.25). The point estimate for the GLSM (RGB-14-X/US-Xgeva) for C_{max} was 1.029 (90% CI 0.96, 1.10), for $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ 1.110 (90% CI 1.04, 1.18). The MAH provided justification that the CIs for AUCs not including unity is not of clinical concern. Overall, bioequivalence acceptance criteria for the co-primary endpoints were met, supporting biosimilarity.

Additional PK parameters included t_{max}, terminal $t_{1/2}$, and partial AUCs ($AUC_{0\text{-}119d}$ and $AUC_{119d\text{-}last}$). Median t_{max} was around 11 days for RGB-14-X and 9 days for US-Xgeva, aligning with the mean t_{max} of 10 days reported for Prolia in the SmPC. Both RGB-14-X and US-Xgeva had a mean terminal half-life of about 6 days, consistent with Prolia's range of 5 to 10 days.

Denosumab levels remained quantifiable until day 252 in 31/81 participants for RGB-14-X and in 21/81 subjects for Xgeva. However, only one subject had an $AUC_{extrap} \geq 20\%$, therefore the selected sampling time period was considered sufficient to allow adequate characterization of the pharmacokinetic profile.

Drug exposure, measured by C_{max}, decreased with higher BMI for both RGB-14-X and US-Xgeva, while AUCs decreased with higher BMI only for Xgeva. These trends, noted in the SmPCs for Prolia and Xgeva, are not clinically significant due to consistent pharmacodynamic effects. Additionally, average denosumab exposure remains consistent across different sites.

Overall, these data support the PK similarity of the test and reference product.

PK in the target population (RGB-14-101)

There were no pre-specified PK endpoints for study RGB-14-101. Mean serum concentration by time point has been provided for the Main Period and the Transition Period. Exposure was slightly higher in the RGB-14-P groups than in the originator group, with the 95% CIs of the geometric mean C_{trough} values overlapping at each time point. Thus, overall comparability of exposure between treatment arms was maintained, even after switching from Prolia to RGB-14-P. Given the sparse PK sampling, further questions on PK parameters would be inconclusive. Therefore, the issue is not further pursued.

Overall, the PK data from the phase 3 study in the target population support equivalence of RGB-14-P to US-Prolia.

Pharmacodynamics

RGB-14-X and RGB-14-P were developed as a biosimilar product to Prolia and Xgeva. Thus, the mechanism of action is identical to the reference products. Denosumab targets RANKL, preventing its interaction with RANK. This action inhibits osteoclast function and reduces their numbers, leading to decreased bone resorption, increased bone mass and strength, and the inhibition of cancer-induced bone destruction. The mechanism of action has been sufficiently described by the applicant. Based on the same mechanism of action of RGB-14-X and RGB-14-P, extrapolation to all approved indications of Prolia and Xgeva has been adequately justified by the MAH.

In studies RGB-14-001 and RGB-14-101, changes in serum C-telopeptide of type I collagen (sCTX) levels were used as a biomarker for bone resorption. This approach is considered state-of-the-art and acceptable. Furthermore, in study RGB-14-101, serum procollagen type I N-propeptide (P1NP) concentrations were additionally measured as a reference marker for bone formation. The timing of PD sample collection was appropriately managed in both studies to assess bone turnover and were previously discussed in the initial

EMA SA. Since CTX is sensitive to circadian rhythms, samples were collected between 7 and 10 am in a fasting state. Samples collected outside this time frame were excluded from the analysis, which is an acceptable methodology.

PD in healthy volunteers (Study RGB-14-001)

In study RGB-14-001, the only PD marker assessed was sCTX. Exclusion of 5 PD samples from 4 subjects from the PD analysis due to PD samples collected outside of the acceptable time window is considered justified. For 6 participants, only partial AUECs could be calculated and were therefore excluded from the AUEC analysis.

Secondary PD endpoints included the percentage change from baseline (%CfB), the area under the effect curve (AUEC) of %CfB in sCTx, and the maximum effect (I_{max}) of sCTx. Descriptive analyses of the mean sCTx (concentration and %CfB) over time showed no significant differences between RGB-14-X and US-Xgeva. After dosing, sCTx levels decreased rapidly and began to rise again approximately 146 days post-dose. At the same time, sCTX-time curves began to separate slightly between the RGB-14-X and US-Xgeva group up to the EOS visit. It is important to note that mean sCTX levels did not return to baseline until the final PD sampling time point and the study duration was insufficient to cover the complete PD profile. On Day 252, the arithmetic mean of %CfB was -38.172% for RGB-14-X and for US-Xgeva -31.043%. Nevertheless. geometric mean AUEC of %CfB in sCTx and I_{max} of sCTx were comparable between the treatment groups. Overall, the PD results support the conclusion on biosimilarity.

PD in the target population (RGB-14-101)

In study RGB-14-101, the AUEC of percent change from baseline in sCTX concentration until week 26 (AUEC of %CfB in sCTX(0-m6)) was chosen as co-primary PD endpoint upon feedback from the EMA (EMA/CHMP/SAWP/338801/2019). Exclusion of three subjects from the PDS were adequately justified.

The co-primary PD endpoint of this study was met: The ratio of the geometric means of the AUEC of %CfB in sCTX concentration for the Main Period between the RGB-14-P and Prolia treatment group was 1.01 with the 95% CIs fully contained within acceptable bioequivalence range (0.978, 1.046).

Secondary PD endpoints, sCTX and P1NP concentrations from baseline to week 78 with their respective median percent change from baseline, supported the primary PD analysis. The mean baseline sCTX and P1NP were similar between treatment groups, and the mean change from baseline in sCTX and P1NP levels were overall comparable between test and reference product at the pre-specified time points (week 4, 26, 52, 78). Overall, the results support the PD biosimilarity of the test and reference product.

Immunogenicity

After single dosing in Study RGB-14-001, no subject was tested ADA positive during the study.

In Study RGB-14-101 in patients with PMO, one subject in the Prolia group was positive for ADA at baseline. In the Main Period, upon dosing, only three subjects (2 subjects in RGB-14-P, one subject in the Prolia group) were found to be treatment induced transient ADA positive until week 52. Two subjects (one each per group) were NAb positive as well. During the Transition period, only one subject in the Prolia/Prolia group had a transient positive ADA and NAb result, whereas no subjects in either the RGB-14-P/RGB-14-P or Prolia/RGB-14-P groups had an ADA positive result from Week 52 to Week 78.

Overall, the observed low immunogenicity with both treatments is in line with the low historical rate of ADAs for Prolia (<1%). There was no impact of ADAs on PK, PD, efficacy and safety until week 78 observed.

2.5.4. Conclusions on clinical pharmacology

In summary, the provided PK and PD data support biosimilarity of RGB-14-X with US-Xgeva and RGB-14-P and US-Prolia.

Considering the similar mechanisms of action, the results of the PK phase I study using RGB-14-X as test product and US-Xgeva as comparator are considered relevant for the demonstration of comparable efficacy between RGB-14-P and Prolia in the efficacy phase III study. Extrapolation of the PK of Prolia and RGB-14-P from the results of the clinical phase I study performed on Xgeva and RGB-14-X appear to be sufficient for determining PK biosimilarity for both sets of reference and test products based on scientific advice from CHMP and PEI and the EMA guideline "Guideline on the investigation of bioequivalence".

2.5.5. Clinical efficacy

Table 17: Clinical efficacy study

Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety								
RGB-14-101	5.3.5.1-bone-disease (Link to synopses)	To demonstrate • similar efficacy and effect of RGB-14-P with US-licensed Prolia on BMD at the lumbar spine at Week 52 in female participants with postmenopausal osteoporosis (PMO) • similar PD (AUEC of %CfB in sCTX) of RGB-14-P with US-licensed Prolia in female participants with PMO To provide additional • comparative efficacy data of RGB-14-P with US-licensed Prolia in female participants with PMO • additional comparative PD data of RGB-14-P with US-licensed Prolia in female participants with PMO To compare • the safety and tolerability of RGB-14-P with US-licensed Prolia in female participants with PMO • the immunogenicity of RGB-14-P with US-licensed Prolia in female participants with PMO	Phase III randomised, double blind, multicentre, multiple fixed dose, two arm parallel group study. Active controlled.	SC injection of RGB-14-P 60 mg (test product) every 26 weeks SC injection of Prolia 60 mg (reference product) every 26 weeks	Main study phase: 473 (RGB-14-P: 242; Prolia: 231) Transition period phase: 188 (RGP-14-P to RGB-14-P: 63; Prolia to RGB-14-P: 62; Prolia to Prolia: 63)	Ambulatory postmenopausal female participants diagnosed with osteoporosis between 60-90 years. Participants had an absolute BMD consistent with T score ≤ 2.5 and ≥ 4.0 at the lumbar spine as measured by DXA during the screening period and at least two lumbar vertebrae (from L1 to L4) had to be evaluable by DXA. Participants had a body weight between 50-90 kg, inclusive, at the screening period.	Main study phase: 52 weeks (Treatment periods 1 and 2) Transition period phase: up to 78 weeks (Treatment period 3)	Complete; Full

AUEC = area under the effective curve; BMD = bone mineral density; BMI = body mass index; DXA = dual energy X ray absorptiometry; EMA = European Medicines Agency; PD = pharmacodynamics; PK = pharmacokinetics; PMO = postmenopausal osteoporosis; RGB-14-P = proposed biosimilar of Prolia; RGB-14-X = proposed biosimilar of Xgeva; SC = subcutaneous; sCTX = serum type I collagen C-telopeptide; US = United States (of America); %CfB = percent change from baseline.

2.5.5.1. Dose response study(ies)

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

2.5.5.2. Main study(ies)

RGB-14-101

Methods

Study RGB-14-P was a randomised, double blind, multicentre, multiple fixed dose, two arm parallel group study to assess the efficacy, pharmacodynamics (PD), safety, tolerability, and immunogenicity of RGB-14-P compared with United States (US)-licensed Prolia in participants with postmenopausal osteoporosis.

There are no ongoing or planned studies.

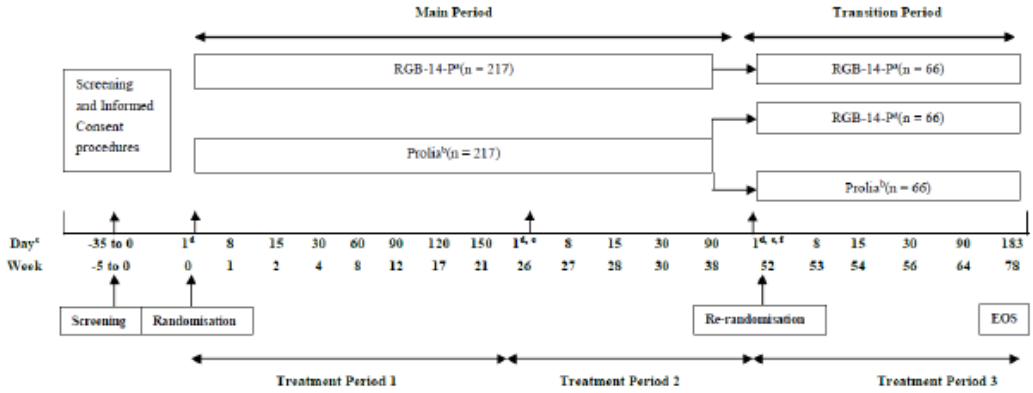
The Main Clinical Study Report was completed based on the data obtained after all participants have either completed the Week 52 study visit or discontinued the study. The data obtained in the Transition Period have been provided as a Final/Supplemental Clinical Study Report during the procedure.

Study phases & Study duration

This study consisted of an up to 35-day Screening Period followed by the Main Period followed by a Transition Period as described below:

- Main Period: The Main Period (52 weeks) consisted of Treatment Period (TP) 1 (26 weeks) and TP 2 (26 weeks). On Day 1 of TP 1, prior to dosing, participants were randomised in a 1:1 ratio to receive either RGB-14-P or Prolia. The IMP was administered on two occasions in a double-blinded manner, on Day 1 of both Treatment Periods 1 and 2 (Weeks 0 and 26).
- Transition Period: The Transition Period consisted of TP 3 (26 weeks); the Transition Period was applicable to a subset of participants. On Day 1 of TP 3 (Week 52) a total of approximately 198 participants were planned to enter the Transition Period. A subset of approximately 132 participants continuing in the Transition Period who received Prolia during the Main Period were to be re-randomised (1:1) to receive either a dose of RGB-14-P or Prolia in a double-blinded manner. A subset of approximately 66 participants continuing in the Transition Period who received RGB-14-P during the Main Period would continue to receive a dose of RGB-14-P but would also follow the randomisation procedure to maintain blinding.

Figure 10: Study Design - Main and Transition Period



Abbreviations: EOS = End-of-Study; n = number of participants.

a. Test product.
b. Reference product.
c. Day(s) refer to days within Screening or Treatment Period.
d. Dosing Visits.
e. Day 1 of Treatment Periods 2 and 3 is also Day 183 of the preceding Treatment Period.
f. Participants continuing to the Transition Period who previously received Prolia during the Main Period were re-randomised 1:1 to either receive RGB-14-P or Prolia in a double-blinded manner. Participants continuing to the Transition Period who received RGB-14-P during the Main Period continued to receive a dose of RGB-14-P but also followed the randomisation procedure to maintain blinding.

The study has been conducted in eight countries (Bulgaria, Czech Republic, Hungary, Italy, Poland, Spain, Ukraine, United States) in a total of 76 active study sites (Poland [25], Bulgaria [19], Hungary [7], Czech Republic and Spain [6 each], Ukraine and United States of America [5 each], and Italy [3]) were activated and screened at least 1 participant.)

Inclusion: Eligible patients were ambulatory postmenopausal women, diagnosed with osteoporosis, with an age range between ≥ 60 and ≤ 90 years at the time of signing the informed consent. Participant had an absolute bone mineral density (BMD) consistent with T score ≤ 2.5 and ≥ 4.0 at the lumbar spine as measured by dual energy X ray absorptiometry (DXA) during the Screening Period and at least two lumbar vertebrae (from L1 to L4) had to be evaluable by DXA.

Exclusion: Postmenopausal women with a history and/or presence of a severe or more than two moderate vertebral fractures; a history or presence of hip fracture; history or presence of atypical femur fracture; an active healing fracture; a bilateral hip replacement; vitamin D deficiency (defined as a serum 25 hydroxyvitamin D level < 50 nmol/L [20 ng/mL]). In such cases, the assessment could be repeated once after vitamin D supplementation (including calcitriol). Participant had hypocalcemia or hypercalcemia (defined as albumin adjusted serum calcium for hypocalcemia < 2.1 mmol/L [8.4 mg/dL] or for hypercalcemia > 2.62 mmol/L [10.6 mg/dL]) at the Screening Period. Participant had a present uncontrolled status of hypothyroidism or hyperthyroidism. Participant had a history (within 5 years prior to Screening) and/or present hypoparathyroidism or hyperparathyroidism other than clinically not significant secondary hyperparathyroidism. Participant had a history and/or presence of osteonecrosis of the jaw (ONJ) or risk factors for ONJ; had a history and/or presence of osteonecrosis of the external auditory canal.

Participant required ongoing use of any osteoporosis treatment (other than calcium and vitamin D supplements). Participant had previously received denosumab or biosimilar denosumab. Participant had previously received: romosozumab, cathesin K inhibitors, strontium or fluoride, intravenous bisphosphonates, oral bisphosphonates within defined periods before screening; other bone active drugs.

Treatments

Duration of Treatment

Main Period: Day 1 of TP 1 and TP 2

Transition Period: Day 1 of TP 3

The approved dose for Prolia is 60 mg administered every 6 months as a subcutaneous injection in the upper arm, upper thigh or abdomen (Prolia Prescribing information). The dose, frequency and route of administration of RGB-14-P were selected to be consistent with that of Prolia for the therapy of women with postmenopausal osteoporosis, as described in the Prolia SmPC and Package Leaflet.

After randomisation, the participants received the first dose of RGB-14-P or Prolia 60 mg via subcutaneous injection (Day 1 of TP 1) and the second dose at Day 1 of TP 2 in the Main Period. A third dose was administered in the Transition Period (Day 1 of TP 3). This third dose was only applicable for a subset of participants. In addition, all participants received at least 1 g of elemental calcium daily and at least 800 IU vitamin D daily.

Table 18: Study Treatments Administered

Arm Name:	**RGB-14-P**	**Prolia**
Intervention Name:	RGB-14-P (test product)	US-licensed Prolia (reference product)
Type:	Drug	Drug
Dosage Formulation:	Pre-filled syringe	Pre-filled syringe
Unit Dose Strength:	60 mg	60 mg
Dosage Level:	60 mg	60 mg
Route of Administration:	Subcutaneous injection	Subcutaneous injection
Use:	Experimental	Active comparator
IMP:	IMP	IMP
Sourcing:	Provided centrally by the Sponsor.	Provided centrally by Parexel.

Arm Name:	RGB-14-P	Prolia
Dosing Instructions:	Main Period: On Day 1 of Treatment Period 1, prior to dosing, participants were randomised in a 1:1 ratio to receive either RGB-14-P or Prolia. Participants received subcutaneous injection of RGB-14-P or Prolia, into the thigh, abdomen or upper arm, administered on Day 1 of Treatment Periods 1 and 2 (Weeks 0 and 26). Transition Period: On Day 1 of Treatment Period 3 (Week 52) a subset of approximately 66 participants in the RGB-14-P dose group followed the randomisation procedure and received one subcutaneous injection of RGB-14-P, into the thigh, abdomen or upper arm. A subset of approximately 132 participants in the Prolia dose group were re-randomised to receive either one subcutaneous injection of RGB-14-P or Prolia into the thigh, abdomen or upper arm. IMP was administered in the morning.	
Device Description:	IMP was provided as a single-dose (1 mL solution) pre-filled syringe made from type I glass with 27-gauge needle, plunger stopper, staked-in needle and needle shield.	IMP was provided as a single-dose (1 mL solution) pre-filled syringe made from type I glass with 27-gauge needle, plunger stopper and needle shield.
Packaging:	Presented in a clear type I glass injection vial (single use) sealed with bromobutyl rubber stopper covered with a fluorinated coating and a plastic flip cap with aluminium sealing.	Presented in a single-dose (1 mL solution) prefilled syringe with a safety guard. The prefilled syringe was not made with natural rubber latex.
Labelling:	IMP was packaged and labelled in accordance with applicable local and regulatory requirements and stored according to the manufacturer's requirements.	IMP was packaged and labelled in accordance with applicable local and regulatory requirements and stored according to the manufacturer's requirements.
Storage:	IMP was stored in a secure area at 2 to 8°C (35.6 to 46.4°F) and in accordance with applicable regulatory requirements.	IMP was stored in a secure area at 2 to 8°C (35.6 to 46.4°F) and in accordance with applicable regulatory requirements.
Manufacturers Batch Numbers:	E15010	1140669 and 1125068

Abbreviations: IMP = investigational medicinal product; US = United States.

Both investigational medicinal products (IMPs), Prolia and RGB-14-P are provided in pre-filled syringes. RGB-14-P is supplied in a single-use disposable, handheld 1 mL long pre-filled syringe with a staked-in needle (27 gauge * % inch). To minimize accidental needlesticks, the syringe is assembled with a BD Ultrasafe Plus™ Passive Needle Guard. Prolia is supplied in a single-use disposable, handheld 1 mL long pre-filled syringe with a staked-in needle (27 gauge * % inch). To minimize accidental needlesticks, the syringe is assembled with BD Ultrasafe Manual Needle Guard.

The estimated duration of the clinical phase for participants in the Main Period from the Screening to the End of Study (EOS) Visit was approximately 13 months and for participants continuing in the Transition Period from the Screening Period until the EOS Visit was approximately 19 months.

Concomitant and rescue therapies

Non-investigational Products

Elemental calcium (at least 1 g per day) and vitamin D (at least 800 IU per day) were given daily from the first day of IMP dosing until the EOS/early termination (ET) Visit.

If hypocalcaemia or hypercalcaemia occurred, the Investigator was to modify dietary intake of calcium and adjust the calcium and/or vitamin D dosage if needed. In such cases, the changes were reported in the eCRF, and hypocalcaemia or hypercalcaemia were reported as an AE if clinically significant.

Intolerance to the non-investigational products could have occurred, especially for calcium. Calcium intolerance could manifest as bloating or constipation. If calcium intolerance occurred, the formulation and/or dose frequency were to be changed to reduce intolerance and increase compliance per the Investigator's discretion.

If intolerance continued after lowering the dose, temporary discontinuation was to be considered. Permanent discontinuation of calcium and/or vitamin D was to be discussed with the Medical Monitor in the contract research organisation (CRO). The Investigator was required to document this in the source data.

Prior concomitant Therapy

Concomitant medications were permitted during this study unless otherwise restricted.

The following medications were prohibited during the study period:

• Any osteoporosis treatment (other than calcium and vitamin D supplements).

• Products containing denosumab (e.g., Xgeva) or biosimilar denosumab.

• Romosozumab.

• Cathepsin K inhibitors.

• Strontium or fluoride (except topical use in toothpaste).

• Intravenous or oral bisphosphonates.

• Teriparatide, abaloparatide or any PTH analogues.

• Tibolone, oral or topical (e.g., transdermal, intravaginal) oestrogen, antioestrogens, SERMs, and aromatase-inhibitors.

• Calcitonin or its derivates and calcimimetics (such as cinacalcet or etelcalcetide).

• Systemic glucocorticosteroids (≥ 5 mg prednisone or equivalent per day for ≥ 10 days or a total cumulative dose of ≥ 50 mg). Topical and inhaled glucocorticosteroids were allowed.

• Other bone active drugs including heparin (also low molecular weight heparins), vitamin K (supplementation or therapeutic dose), vitamin K antagonists (eg, warfarin, acenocumarol), emtricitabine, tenofovir, adefovir, anticonvulsants (with the exception of benzodiazepines, gabapentin and pregabalin), systemic ketoconazole, ACTH, lithium, protease inhibitors, GnRH agonists, anabolic steroids.

• Invasive dental procedures (eg, dental implants or oral surgery) and major surgeries or bone surgeries (unless required for AE/SAE management after careful consideration) were prohibited during the study period.

Objectives

Primary objective:

Efficacy: To demonstrate similar efficacy and effect of RGB-14-P with US-licensed Prolia on BMD at the lumbar spine at Week 52 in female participants with postmenopausal osteoporosis

Pharmacodynamics: To demonstrate similar pharmacodynamics (AUEC of %CfB in sCTX) of RGB-14-P with US-licensed Prolia in female participants with postmenopausal osteoporosis (based on EMA scientific advice)

Key secondary objectives:

- *Efficacy:* To provide additional comparative efficacy data of RGB-14-P with US-licensed Prolia in female participants with postmenopausal osteoporosis
- *Pharmacodynamics:* To provide additional comparative pharmacodynamic data of RGB-14-P with US-licensed Prolia in female participants with postmenopausal osteoporosis

Other secondary objectives:

- Safety: To compare the safety and tolerability of RGB-14-P with US-licensed Prolia in female participants with postmenopausal osteoporosis
- Immunogenicity: To compare the immunogenicity of RGB-14-P with US-licensed Prolia in female participants with postmenopausal osteoporosis

Outcomes/endpoints

Primary Efficacy Endpoint:

Efficacy: **%CfB in lumbar spine BMD** at Week 52

Pharmacodynamics: **AUEC of %CfB sCTX0-m6** until Week 26 (secondary for USFDA submission)

Key secondary endpoints:

Efficacy

- %CfB in total hip BMD at Weeks 26, 52, and 78
- %CfB in lumbar spine BMD at Weeks 26, 52, and 78
- %CfB in femoral neck BMD at Weeks 26, 52, and 78
- Vertebral fragility fracture incidence at Weeks 52 and 78
- Non-vertebral fragility fracture incidence at Weeks 52 and 78

Pharmacodynamics

- %CfB in serum P1NP at Weeks 4, 26, 52, and 78
- %CfB in sCTX at Weeks 4, 26, 52, and 78

Other secondary endpoints:

Safety

- AEs, SAEs, clinical laboratory safety assessments (haematology, clinical chemistry and urinalysis), vital signs, physical examination, ECG, injection site reaction and fracture assessment up to Week 78

Immunogenicity

- Incidence of binding ADAs and NAbs at Weeks 0, 2, 4, 26, 28, 30, 52, 54, 56, and 78
- Titre determination of binding ADAs at Weeks 0, 2, 4, 26, 28, 30, 52, 54, 56, and 78

Table 19: Estimands for primary objective

Population	**Postmenopausal Women with Osteoporosis receiving the IMP on two occasions in a double-blinded manner, on Day 1 of both TPs 1 and 2 (Weeks 0 and 26).**
Treatment condition<s>	RGB-14-P compared to US-Prolia
Endpoint (variable)	%CfB in lumbar spine BMD (g/cm2) at Week 52. AUEC of %CfB sCTX0 m6 until Week 26
Population-level summary	Difference of means between the test and reference arms in change from baseline BMD: δ = μRGB-14-P -μProlia μRGB: BMD mean %CfB in RGB-14-P study arm μProlia: BMD mean %CfB in Prolia study arm
Intercurrent events and strategy to handle them	
ICE1: The first and/or the second dose of randomised IMP is not administered.	Treatment policy strategy will be applied: All obtained data points will be included in the analysis, in line with the ITT-principle. Principal stratum causal estimand strategy will be used: Only patients who would not experience either ICE if exposed to either treatment are relevant to the clinical question. To control the validity of the estimand dropout and ICE rates and reasons will be monitored.
ICE2: The participant	Composite variable strategy will be applied: Intercurrent event is considered to be informative about the outcome, so that the responses obtained after ICE

Population	Postmenopausal Women with Osteoporosis receiving the IMP on two occasions in a double-blinded manner, on Day 1 of both TPs 1 and 2 (Weeks 0 and 26).
received other medication	occurrence will be imputed under the null hypothesis. In other words, responses obtained after ICE occurrence will be imputed with multiple imputation techniques so that outcomes observed after ICE2 occurrence will be modelled under the null hypothesis. Principal stratum causal estimand strategy will be used: Only patients who would not experience either ICE if exposed to either treatment are relevant to the clinical question. To control the validity of the estimand dropout and ICE rates and reasons will be monitored.

The primary endpoint will be analysed following the framework of the estimand concept as detailed in the latest International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials guidance [3]. From this end, efficacy analysis will be defined with terms used for the estimand concept.

Handling of intercurrent events

ICE 1, the first and/or the second dose of randomised IMP is not administered, will be handled under treatment policy strategy: all obtained data points will be included in the analysis, in line with the ITT principle.

ICE 2 will consist of the participant receiving other medication alongside the IMP, which affects the primary variable, i.e., prohibited therapies as per SAP. Composite variable strategy will be applied; Intercurrent event is considered to be informative about the outcome, so that the responses obtained after ICE occurrence will be imputed under the null hypothesis. Details about strategy implementation for EMA and FDA submissions are outlined here below. Descriptive analysis of the number, proportion and timing of intercurrent events (ICEs) will be presented.

Sample size

Approximately 434 women with postmenopausal osteoporosis were planned to be enrolled 1:1 (217 participants per arm, including 17% drop-out) in the study to have 362 evaluable participants to evaluate the primary efficacy endpoint at 90% power during the Main Period. Participants were stratified by previous use of bisphosphonates and geographical region.
Based on a meta-analysis of 3 different studies conducted with denosumab, sample size was calculated from the following parameters:

- The primary parameter is the %CfB in lumbar spine BMD
- Two-sided 95% CIs of the difference between the study arms must be contained within the equivalence margin of ± 1.45

- The expected (true) value of the primary parameter in the reference arm is equal to 5.35
- The expected (true) difference between the study arms equal -0.2675 (i.e., 5% of the expected reference arm value)
- The expected (true) common standard deviation is 3.44

Based on the above assumptions the total evaluable sample size required for efficacy comparison with a margin of 1.45%, power of 90% is 362 (181 per arm). Calculating with dropout rate of 1/6, 217 participants per arm were planned to be recruited in the planned comparative efficacy study. Although theoretically dropout should not be applied for the Treatment Policy Estimand, its use in the study is supported by the uncertainty of the variance of the primary parameter among different estimands, and by the fact that even if all the 2 × 217 = 434 participants are evaluable, the power will stay below 95%.

Randomisation and blinding (masking)

Randomisation:

At randomisation (TP 1, Day 1) all eligible participants were randomised via Interactive Response Technology (IRT) to one of the treatment groups. The IRT assigned a randomisation number and specified a unique medication number for the first package of IMP to be dispensed to the participant.

The randomisation numbers were generated using the following procedure to ensure that treatment assignment was unbiased and concealed from participants and Investigator staff. A participant randomisation list was produced by the IRT provider using a validated system that automated the random assignment of enrolment (participant) numbers to randomisation numbers. In effect there was a separate randomisation list for each stratum (combination of geographical region and prior bisphosphonate use). These randomisation numbers were lined to the different treatment groups, which in turn were linked to medication numbers.

Blinding and Unblinding:

Upon completion of Week 52 period, an interim data freeze will happen, with consequent unblinding of a restricted team as per below explained strategy. Final Data Base Lock (DB Lock) will happen upon completion of Week 78 period; after final DB Lock, there will be general unblinding.

CRO main team employees will remain blinded to the assignment of study treatment during Main Period and Transition Period until final database lock for the Transition Period.

For the production and review of the Week 52 unblinded delivery, including unblinded Tables Listings and Figures (TFLs) and Clinical Study Report, separate independent unblinded teams will be assigned at CRO and at Sponsor.

Additional measure to prevent unauthorized unblinding:

- Protocol Deviations (PDs) logs will be blinded by independent personnel (PDT ID and Subject Number columns removed) and reviewed by the bioanalytical team in a blinded manner.

Individuals unblinded to participant-level treatment allocation at Week 52 readout will not be directly involved in communications with clinical study sites after they are unblinded.

Clinical study sites, except unblinded site staff who manages Investigational Medical Product (IMP) related unblinded activities, and patients will be kept blinded both during Main Period and Transition Period; the same will be true for CRO's blinded clinical team. In order to be able to prevent bias for the treatment comparison at Week 78, site contacts during this period will be handled by study blinded CRAs (Clinical

Research Associate) and blinded COLs (Clinical Operations Leaders) who will remain blinded to participant-level treatment allocation at all times during the conduct of the study.

This study was double blinded to eliminate observer or performance bias. Participants, Investigators, and other study personnel were unaware of the treatment group assignments throughout the study period.

Since the IMP pre-filled syringes were not blinded, the pharmacy staff and monitor responsible for checking IMP accountability were unblinded. Unblinded site staff did not perform any clinical assessment.

Part of CRO and Sponsor's personnel were unblinded after database lock for the 12-month Main Period and as such were not in direct contact with the sites or involved in any treatment decisions during the Transition Period. Details of the blinding strategy are described in the Blinding Maintenance Plan.

Unblinding was considered only when knowledge of the treatment assignment was deemed essential for the participant's safety by the Investigator or regulatory body.

Two different Blinded Data Review Meetings (BDRM) and database locks (DB Lock) will happen, one covering the main period and one covering the transition period. General unblinding will happen after the last DB Lock, i.e., the transition period one. A separate unblinded team may be assigned at CRO to proceed with unblinding TFLs production in between the two DB Locks.

Statistical methods

Analysis sets:

Table 3 – Populations for Analysis

Population (Analysis Set)	Description
ENR	All participants who signed the informed consent form (including screening failures). Participants will be reported according to their randomised treatment in each period.
FAS	The FAS comprises all participants to whom the IMP has been randomised. In the transition period, the FAS will be intended as all participants to whom the IMP has been re-randomised in transition period. Note: subjects excluded from the main period FAS, will not be included in the transition period FAS. Participants will be analysed according to their randomised treatment in each period.
PPS	The PPS comprises a subset of the FAS. A participant will be completely excluded from the PPS in case of protocol deviations which can affect interpretability of the primary endpoint analysis. Note: dropout subjects will not be excluded in the PPS due to their early discontinuation. In the transition period, the PPS consists of the main period PPS subjects who received full or partial dose of 3rd IMP injection; further criteria for exclusion from transition period PPS may be identified at the BDRM prior than DB Lock of the data from the transition period. Note: subjects excluded from the main period PPS, will not be included in the transition period PPS. Participants will be analysed according to the treatment actually received in each period.
SAF	The SAF consists of all participants who received at least one full or partial dose of IMP. Participants will be analysed according to the IMP they actually received at Day 1 Treatment period 1. In the transition period, the SAF consists of all participants who received full or partial dose of 3rd IMP injection. Participants will be analysed according to the IMP they actually received as the 3rd dose (Treatment Period 3). Note: subjects excluded from the main period SAF, will not be included in the transition period SAF.
PDS	The PDS consists of all participants in the safety population with at least one evaluable pharmacodynamic parameter (%CfB and AUEC) and do not have any protocol deviations that

	have a relevant impact on sCTX or serum P1NP results included in the pharmacodynamic parameter calculation (see Section 4.3). In the transition period, the PDS consists of all participants who received full or partial dose of 3rd IMP injection, had at least one evaluable pharmacodynamic parameter post 3rd IMP injection and do not have any protocol deviations that may have a relevant impact on sCTX or serum P1NP results included in the pharmacodynamic parameter calculation (see Section 4.3). Note: in general, subjects excluded from the main period PDS due to protocol deviations, will not be included in the transition period PDS. Final decision will be consolidated prior to DB Lock. PDs with possible relevant impact on sCTX or serum P1NP will be identified prior to DB Lock of data from the main and the transitions period. Patients will be analysed according to the IMP they actually received at Day 1 Treatment Period 1 (for main period) and Treatment Period 3 (for transition period).
IAS	The IAS consists of all participants in the safety population who have the pre-dose immunogenicity result and at least one available post-baseline immunogenicity assessment and do not have any protocol deviations that have a relevant impact on immunogenicity evaluations. In the transition period, the IAS consists of all participants who received full or partial dose of 3rd IMP injection, had at least one available immunogenicity assessment post 3rd IMP injection and do not have any protocol deviation that may have a relevant impact on immunogenicity evaluations. Of note: subjects excluded from the main period IAS due to protocol deviations, will not be included in the transition period IAS. Final decision will be consolidated prior to DB Lock. PDs with possible relevant impact on immunogenicity evaluations will be identified prior to DB Lock of data from the main and the transitions period. Patients will be analysed according to the IMP they actually received at Day 1 Treatment Period 1 (for main period) and Treatment Period 3 (for transition period).

AUEC = area under the effective curve; %CfB = percentage change from baseline; ENR = Enrolled Analysis Set; FAS = Full Analysis Set; IAS = Immunogenicity Analysis Set; IMP = investigational medicinal product; P1PN = procollagen type 1N-terminal propeptide; PDS = Pharmacodynamic Analysis Set; PPS = Per Protocol Analysis Set; SAF = Safety Analysis Set; SAP = Statistical Analysis Plan; sCTX = serum type I collagen C-telopeptide

FAS was used for demographic and baseline characteristics, medical history, medications and efficacy analyses (with the exception of secondary estimand). PPS was used for efficacy secondary estimand.

Analysis strategy for primary endpoint

A model of ANCOVA was implemented to estimate the difference in means between the test and reference arms for percentage CfB of BMD in the lumbar spine at Week 52. All ANCOVA models (also applied for secondary endpoints) were performed with covariates of treatment arm (RGB-14-P and Prolia), stratification factors at randomisation (previous use of bisphosphonates [yes/no]) and geographical region (Europe, US), machine type, baseline value of the dependent variable, and machine type*baseline value of dependent variable interaction.

Analysis strategy for secondary endpoints

For the analysis of secondary endpoints, a model of ANCOVA or a mixed model for repeated measures (MMRM) was used.

The ANCOVA model was specified as for the primary analysis.

All MMRM were performed with covariates of treatment arm (RGB-14-P and Prolia), stratification factors at randomisation (previous use of bisphosphonates [yes/no]) and geographical region (Europe, US), machine type, baseline value of the dependent variable, machine type*baseline value of dependent variable interaction, study week, and study week*treatment arm interaction. Unstructured covariance matrix was used. In case of convergence issues, alternative structures was considered in the following order:

Autoregressive(1), Compound Symmetry, Toeplitz; until convergence is met. MMRM will be executed without MI applied, without special handling of ICEs.

Handling of withdrawals, discontinuations or missing data

Primary endpoint: For the primary estimand missing data was assumed to be MCAR and was not imputed. For the secondary estimand MI was used.

Missing data without experiencing ICE2 will be assumed to be MCAR and will not be imputed.
Assessments of the primary endpoints observed after occurrence of ICE2 will be disregarded, i.e., artificially set as missing, and will be replaced with MI techniques.
Different assumptions will be made for handling of ICE2 in each of the two arms. Under Prolia group, data artificially set as missing after ICE2 occurrence will be assumed to be MAR and imputed assuming they would have behaved like subjects in the same arm had they not taken prohibited medication. Under the RGB-14-P group, Week 52 data artificially set as missing after ICE2 occurrence will be imputed using MNAR method 'Under the Null': after ICE2 primary efficacy data are assumed to worsen from "MAR" by an amount of equivalence margin "delta". The equivalence margin of -1.45% will be used as the "delta" for the ICE2 in the RGB-14-P group.
Secondary endpoints: No imputation of missing data was foreseen for secondary endpoints.

Sensitivity analyses

1. Missing primary efficacy post baseline data will be imputed as a sensitivity estimation. As sensitivity analysis, missing data will be imputed in accordance with techniques proposed by Jakobsen et al (2017): if the proportion of non-complete cases is below 5%, sensitivity analysis will be not conducted.
   Missing data will be assumed to be MAR and imputed using fully conditional specification (FCS) method via SAS PROC MI. Additionally, likewise for the primary endpoint primary estimand analysis, assessments of the primary endpoints observed after occurrence of ICE2 will be disregarded, i.e., artificially set as missing, and will be replaced with MI techniques. Different assumptions will be made for handling of ICE2 in each of the two arms (already described above).
   MI will be performed through SAS PROC MI, variables used to impute Week 52 missing values will be the dependent variables from ANCOVA model; additionally, Week 26 data will be used as well in the SAS PROC MI as a post-randomization predictive variable; in that contest the missing Week 26 (originally or post-ICE2 assessments) will be imputed as well within the SAS PROC MI itself, with MAR approach for both the treatment arms. Below steps will be followed (note: the steps below will be executed on a copy of the BMD %CfB column variable, while the original will be maintained as well):

   Step 1) In a copy of the whole original efficacy dataset, the Week 26 and Week 52 %CfB observed after ICE2 occurrence will be set as missing

   Step 2) Two datasets, one including only Prolia subject and another one including only RGB-14-P, will be filtered from the dataset resulting from Step 1

   Step 3) In the Prolia dataset created in Step 2, Week 52 %CfB missing or assessed after ICE2 occurrence will be imputed as MAR. SAS PROC MI will be executed with FCS method, 50 complete datasets will be created, seed 252679 will be used, variables used to impute missing values will be the stratification factors (previous use of bisphosphonates and geographical region), baseline BMD, machine type and Week 26 lumbar spine BMD %CfB

Step 4) In the RGB-14-P dataset created in Step 2, Week 52 %CfB missing or assessed after ICE2 occurrence will be imputed as MAR. SAS PROC MI will be executed with FCS method, 50 complete datasets will be created, seed 252679 will be used, variables used to impute missing values will be the stratification factors (previous use of bisphosphonates and geographical region), baseline BMD, machine type and Week 26 lumbar spine BMD %CfB. To be able to impute 'Under the Null' the Week 52 post ICE2 occurrence values, the MNAR statement will be used including ADJUST option with SHIFT and ADJUSTOBS as sub options, allowing a shift of -1.45 to be applied to only the value imputed after occurrence of ICE2.

Step 5) MI datasets resulting from Steps 3 and 4 will be compiled in a unique dataset

Step 6) The primary efficacy ANCOVA model as defined at section 4.2.1.2.1 will be executed by imputation on complete dataset obtained in Step 5

Step 7) Estimates from the Step 6 will then be combined through SAS MIANALYZE, first type error alpha will be set at 5%. Combined estimation of the difference RGB 14- P – Prolia will be examined together with the corresponding two-sided 95% CI. Equivalence of RGB 14-P compared to Prolia will be suggested if the LCL will be greater than -1.45 and the UCL will be less than 1.45.

2. Secondary estimand sensitivity tipping point analysis

3. Supplementary analysis - hypothetical ICE handling strategy

The supplementary estimand of BMD %CfB at Week 52 will utilise a hypothetical ICE handling strategy as if the ICE did not occur, as a further, sensitive, investigation into whether differences in outcomes would emerge if the whole study population were fully compliant with treatment.

Data points captured after the ICE will be left out from the FAS analysis. The same ICEs will be applied as for the primary and secondary estimands.

Primary endpoint will be analysed by using MMRM with the following factors:

- Treatment (RGB-14-P and US-licenced Prolia®, as planned treatment)
- Stratification factors for randomisation:
    - o Previous use of bisphosphonates (yes/no)
    - o Geographical region (Europe, US)
- Baseline BMD value
- Machine type (as per DXA scan external data transfer)
- Machine type * Baseline BMD value interaction
- Study Week (Week 26 and Week 52 will be included in the model)
- Study Week (Week 26 and Week 52) * Treatment interaction

Unstructured covariance matrix will be used. In case of convergence issues, alternative structures will be considered in the following order: Autoregressive(1), Compound Symmetry, Toeplitz; until convergence is met.

Missing data will be assumed to be MCAR and will not be imputed.

There was no interim analysis planned in this study.

Results

Participant flow

Extent of Exposure

Of the 473 participants (242 in the RGB-14-P group and 231 in the Prolia group) who were randomised, all received the first injection of RGB-14-P or Prolia, and 446 (227 [93.8%] in the RGB-14-P group and 219 [94.8%] in the Prolia group) received the second injection of RGB-14-P or Prolia. A total of 27 (5.7%) participants (15 [6.2%] in the RGB-14-P group and 12 [5.2%] in the Prolia group) did not receive the second injection mainly due to reasons such as withdrawal by participant, AE and lost to follow-up.

Overall, postmenopausal women fulfilled the inclusion criteria. Major deviations with respect to exclusion criteria were related to meeting an exclusion criterion in 3 participants and 'other' criteria (involved into another study) in 1 participant, that led to exclusion from the PPS (RGB 14-P: 2 participants and Prolia: 2 participants).

Withdrawal from study: A total of 37 (7.8%) randomised patients (RGB-14-P 17 patients; RP 20 patients) were withdrawn in the main period for the following reasons: Withdrawal by subject 8 patients in the RGB-14-P group, 13 patients in RP group; adverse events 2 patients in each treatment group, lost to follow-up 3 patients in the RGB-14-P group; death 1 patient in the RP group; protocol deviation 1 patient in the RGB-14-P group; other reasons 2 patients in each treatment group. For three patients in Ukraine the reasons for end of treatment were not reported (due to the war).

Table 20: Exposure - Main Period (Full Analysis Set for Main Period)

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
First injection not received	n (%)	0	0	0
First injection received	n (%)	242 (100)	231 (100)	473 (100)
Full dose	n (%)	242 (100)	231 (100)	473 (100)
Partial dose	n (%)	0	0	0
Second injection not received	n (%)	15 (6.2)	12 (5.2)	27 (5.7)
Second injection received	n (%)	227 (93.8)	219 (94.8)	446 (94.3)
Full dose	n (%)	227 (93.8)	219 (94.8)	446 (94.3)
Partial dose	n (%)	0	0	0

Abbreviations: N = number of subjects in the analysis set; n = number of subjects in the specific category.

%: calculated using the number of subjects in the analysis set as the denominator (n/N*100).

Source: Table 14.1.8.1

Disposition of patients

A total of 1211 participants were screened in the study, 41 of which were re-screened, Out of which, 473 participants were randomised (242 participants in the RGB-14-P treatment group and 231 in the Prolia treatment group). All randomised participants received the IMP and 436 (92.2%) participants completed the Main Period of the study.

Among participants who completed the Main Period, 188 participants entered the Transition Period, including 63 participants continuing RGB-14-P treatment, 62 participants from the Prolia group re-randomised to RGB-14-P treatment, and 63 participants from the Prolia group re-randomised to Prolia treatment. Most participants completed the Transition Period, with the exception of 1 (1.6%) in the Prolia-to-Prolia group who withdrew from the study.

The percentage of participants who completed the Main Period was comparable between the two treatment groups (RGB-14-P: 225 [93%] participants and Prolia: 211 [91.3%] participants).

The most common primary reason for study discontinuation in the Main Period was withdrawal by subject (23 [4.9%] participants).

Overall, 4 (0.8%) participants discontinued the study due to an AE and one (overall, 0.2%) participant discontinued the study due to death.

The geopolitical conflict posed significant challenges to the conduct of the study in Ukraine. The Sponsor terminated the study in Ukraine because IMP shipment and blood sample shipment to the Central Laboratory could not be ensured. All transportation possibilities were interrupted in February and March 2022. In addition, the Sponsor had concerns that due to the uncertain political situation, safety of the participants and CRAs was compromised. All screening activities and the randomisation were suspended. The continuation of the treatment was decided on a case-by-case basis considering the ever-prevailing circumstances. The reason for end of treatment was not reported for three participants.

Figure 11: Study RGB-14-101: Patient disposition – Main and Transition Period

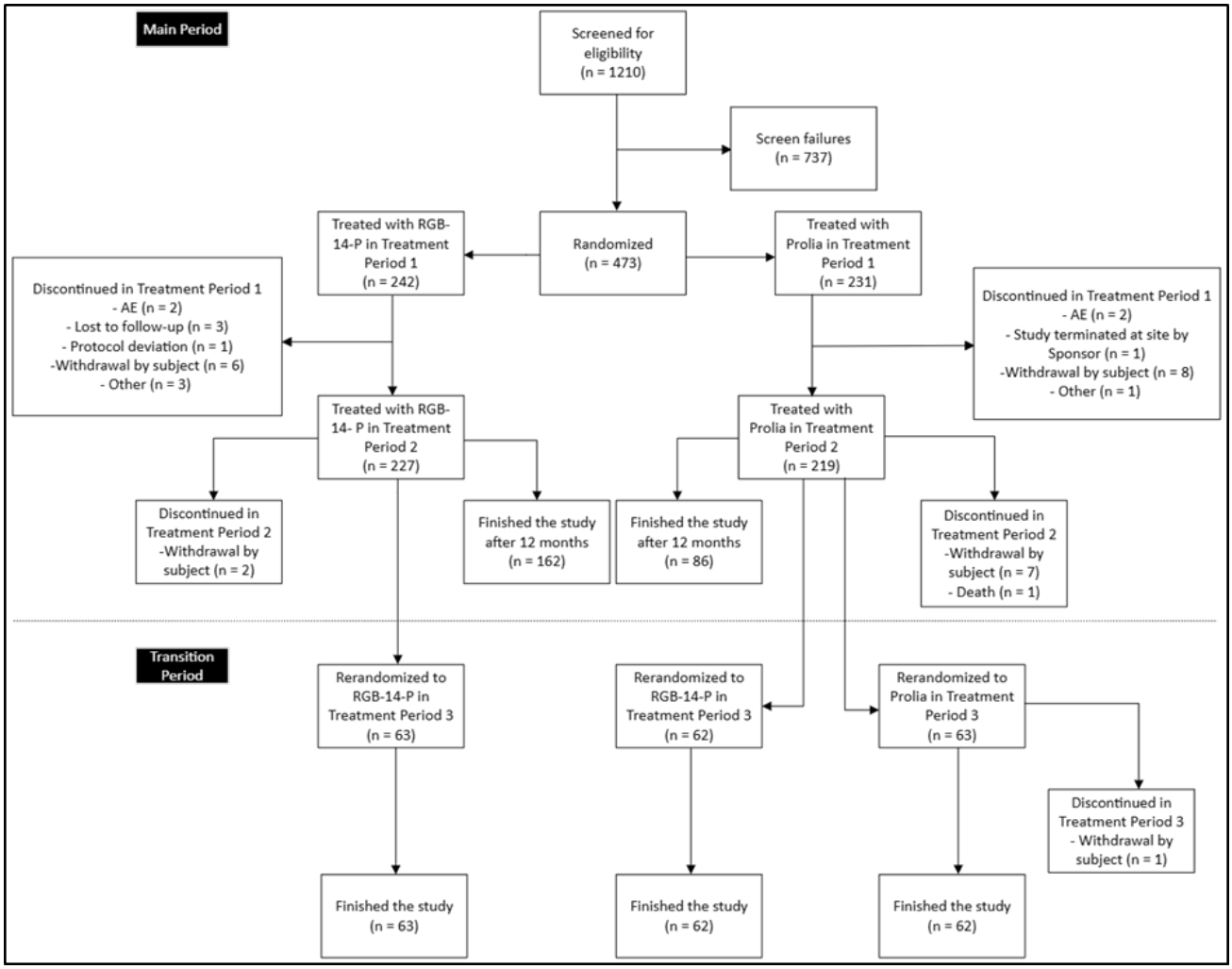


Table 21: Subject Disposition - Main Period (Enrolled Analysis Set)

Enrolled Analysis Set				1211
Screen Failures				738
Subject Randomised (Full Analysis Set)	n (%)	242 (100)	231 (100)	473 (100)
Subjects Dosed (Safety Analysis Set)	n (%)	242 (100)	231 (100)	473 (100)
Pharmacodynamic Analysis Set	n (%)	241 (99.6)	229 (99.1)	470 (99.4)
Immunogenicity Analysis Set	n (%)	239 (98.8)	228 (98.7)	467 (98.7)

Per Protocol Analysis Set	n (%)	240 (99.2)	229 (99.1)	469 (99.2)
Subjects Completed	n (%)	225 (93.0)	211 (91.3)	436 (92.2)
Treatment Policy Estimand	n (%)	242 (100)	231 (100)	473 (100)
Principal Stratum Estimand	n (%)	216 (89.3)	206 (89.2)	422 (89.2)
Randomised Subjects Withdrawn in the Main Period	n (%)	17 (7.0)	20 (8.7)	37 (7.8)
Reason for End of Treatment*				
Withdrawal by Subject	n (%)	8 (3.3)	13 (5.6)	21 (4.4)
Adverse Event	n (%)	2 (0.8)	2 (0.9)	4 (0.8)
Lost to Follow-up	n (%)	3 (1.2)	0	3 (0.6)
Death	n (%)	0	1 (0.4)	1 (0.2)
Protocol Deviation	n (%)	1 (0.4)	0	1 (0.2)
Other	n (%)	2 (0.8)	2 (0.9)	4 (0.8)
Other: An Exclusion Criterium has Been Found - More Than Three Years of Cumulative Use of Oral Bisphosphonates Prior the Screening Period.	n (%)	1 (0.4)	0	1 (0.2)
Other: Study Objective Confounded by Monoclonal Gammopathy	n (%)	1 (0.4)	0	1 (0.2)
Other: Subject's Personal Reason	n (%)	0	1 (0.4)	1 (0.2)
Other: The Patient for a Personal Reason Cannot Attend an Appointment for Too Long	n (%)	0	1 (0.4)	1 (0.2)
Reason for End of Study				
Completed	n (%)	162 (66.9)	86 (37.2)	248 (52.4)
Withdrawal by Subject	n (%)	8 (3.3)	15 (6.5)	23 (4.9)
Adverse Event	n (%)	2 (0.8)	2 (0.9)	4 (0.8)
Lost to Follow-up	n (%)	3 (1.2)	0	3 (0.6)
Study Terminated by Sponsor	n (%)	1 (0.4)	1 (0.4)	2 (0.4)
Death	n (%)	0	1 (0.4)	1 (0.2)
Inclusion/Exclusion Criteria Not Met	n (%)	1 (0.4)	0	1 (0.2)

Protocol Deviation	n (%)	1 (0.4)	0	1 (0.2)

Abbreviations: eCRF = electronic case report form; N = number of subjects with each treatment, for the overall study group it is the number of subjects in the Enrolled Analysis Set; n = number of subjects in specific category.

%: calculated using the number of subjects with each treatment, or the Enrolled Analysis Set for the overall study group, as denominator (n/N*100).

*Reason for end of Treatment was not reported for patients [redacted], [redacted] and [redacted]. Number of subjects who completed Main Period, did not match with number of completed in end of study as a portion of patients continued in the Transition Period and did not complete end of study page in eCRF while in Main Period.

Source: Table 14.1.1.1

Protocol Deviations

Protocol deviations were assessed and categorised in accordance with a Protocol Deviation Specification Document. Based on the description of each event, protocol deviations were assessed whether it would impact the completeness, accuracy, and/or reliability of key (or critical) protocol identified data or processes, as well as whether it would impact a participant's rights, safety, or well-being. In the Protocol Deviation Specification Document thresholds were set according to which decision was taken during assessment meetings, whether a protocol deviation was significantly important, and has unblinding potential. Most important protocol deviation categories are listed in the table below.

A total of 137 (29%) participants in the FAS had major protocol deviations. The most common category of major protocol deviation was procedures/tests in 112 (23.7%) participants overall. The laboratory was asked to perform additional tests. Sites deviated from the process that was described in the Laboratory manual. There was no impact on data integrity. Overall, 1 (0.2%) participant had major protocol deviation due to AE SAE.

A total of 4 participants had major deviations that led to exclusion from the PPS (RGB-14-P: 2 participants and Prolia: 2 participants), which were related to the category of meeting an exclusion criterion in 3 participants and to 'other' criteria (involved into another study) in 1 participant.

A total of 3 participants had major deviations that led to exclusion from the pharmacodynamic analysis set (PDS) (RGB-14-P: 1 participant and Prolia: 2 participants), which were all related to procedures and tests.

The major protocol deviations for the below listed protocol deviation terms were excluded from summary tables and statistical analysis of the samples at the timepoint at which the protocol deviation occurred:

- Serum CTX sample collection time was not prior to IMP administration at same visit.
- Serum CTX and P1NP lab sample deviation (including sample not evaluable).
- Participant was not fasting for sCTX sample collection.
- Serum CTX sample collection time was not between 07:30 and 10:00 a.m.

A total of 27 (5.7%) participants (RGB-14-P: 15 [6.2%] participants and Prolia: 12 [5.2%] participants) experienced an ICE1 (the first and/or the second dose of the randomised IMP was not administered) where second dose of the randomised IMP was not administered. A total of 14 (3%) participants (RGB-14-P: 6 [2.5%] participants and Prolia: 8 [3.5%] participants) experienced an ICE2 (the participant received other medication alongside the IMP, which affects the primary variable) where the first occurrence of ICE2 was in TP 1. A total of 11 (2.3%) participants (RGB-14-P: 5 [2.1%] participants and Prolia: 6 [2.6%] participants) had ICE2 where the first occurrence of ICE2 was in TP 2. The ICE1 and ICE2 were comparable between the RGB-14-P and Prolia treatment groups.

One participant in the RGB-14-P treatment group had a minor protocol deviation related to COVID-19. (TP1 Day 15 visit was not performed as scheduled [TP1 Day 1 + 14 ±1 day]).

Table 22: Protocol Deviations and Intercurrent Events - Main Period (Full Analysis Set for Main Period)

Table 14.1.2.1 Protocol Deviations and Intercurrent Events - Main period (Full Analysis Set for Main Period)

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Any Protocol Deviation (PD)	n (%) E	211 (87.2) 1074	204 (88.3) 1259	415 (87.7) 2333
Any Major PD	n (%) E	65 (26.9) 131	72 (31.2) 126	137 (29.0) 257
Any Covid-19 related PD	n (%) E	1 (0.4) 1	0	1 (0.2) 1
Any Major Covid-19 related PD	n (%) E	0	0	0
Any ICE	n (%) E	26 (10.7) 29	25 (10.8) 39	51 (10.8) 68
ICE1	n (%)	15 (6.2)	12 (5.2)	27 (5.7)
First dose of randomised IMP not administered	n (%)	0	0	0
Second dose of randomised IMP not administered	n (%)	15 (6.2)	12 (5.2)	27 (5.7)
ICE2	n (%) E	11 (4.5) 14	14 (6.1) 27	25 (5.3) 41
First occurrence of ICE2 was in treatment period 1	n (%)	6 (2.5)	8 (3.5)	14 (3.0)
First occurrence of ICE2 was in treatment period 2	n (%)	5 (2.1)	6 (2.6)	11 (2.3)

ICE: Intercurrent Event; IMP: Investigational Medicinal Product.
ICE1: The first and/or the second dose of randomised IMP is not administered.
ICE2: The participant received other medication alongside the IMP, which affects the primary variable.
N: The number of subjects in the analysis set; n: The number of subjects with Protocol Deviations in the specific category; E: number of Protocol Deviations in the specific category; %: calculated using the number of subjects in the analysis set as the denominator (n/N*100).
Reference listing: 16.2.2, 16.2.3.2.1

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Table 23: Major Protocol Deviations - Main Period (Full Analysis Set)

	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Any Major Protocol Deviation	n (%) E	65 (26.9) 131	72 (31.2) 126	137 (29.0) 257
Procedures/Tests	n (%) E	53 (21.9) 106	59 (25.5) 102	112 (23.7) 208
Visit Schedule	n (%) E	10 (4.1) 14	8 (3.5) 9	18 (3.8) 23
IP Admin/Study Treat	n (%) E	4 (1.7) 4	6 (2.6) 6	10 (2.1) 10
Inc/Excl Criteria	n (%) E	3 (1.2) 3	1 (0.4) 1	4 (0.8) 4
Informed Consent	n (%) E	2 (0.8) 2	4 (1.7) 4	6 (1.3) 6
Other	n (%) E	2 (0.8) 2	3 (1.3) 3	5 (1.1) 5
AE SAE	n (%) E	0	1 (0.4) 1	1 (0.2) 1

Abbreviations: AE = adverse event; E = number of Protocol Deviations in the specific category; IP = investigational product; N = number of subjects in the analysis set; n = number of subjects with Protocol Deviations in the specific category; SAE = serious adverse event.

%: calculated using the number of subjects in the analysis set as the denominator (n/N*100).

The same patient may have had more than 1 Important Protocol Deviation.

Source: Table 14.1.2.1.1

Recruitment

Date of First Enrolment: 21 Sep 2021

Date of Last Patient Completed: 02 Oct 2023

Week 52 Database Lock Date: 14 Dec 2023

Week 78 Data Base Lock Date: 13 Feb 2024

Conduct of the study

The original protocol (dated 10 Mar 2021) was amended five times (three times substantially and two times non-substantially). A summary of overall rationale of each protocol amendment is provided below.

Non-substantial Amendment 1: 20 Jul 2021

This amendment was considered to be non-substantial because it neither significantly impacted the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The protocol was amended to incorporate and implement responses and suggestions made by the Czech Republic Regulatory Authority.

Substantial Amendment 1: 03 Aug 2021

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The protocol was mainly amended to incorporate and implement responses and suggestions made by the USFDA.

Changes in inclusion/exclusion and discontinuation criteria:

• Text added on inclusion/exclusion of participants with a history of childhood rickets.

• Text added to specify described uncontrolled hypothyroidism and hyperthyroidism.

• Text added to further clarify exclusion criteria with regards to ONJ.

• Updated to excluded medication prior to and during the study.

• Text added to address management of reduction in BMD below a pre-defined threshold that may occur during the study.

• Text added to establish individual stopping criteria (eg, life-threatening treatment-related hypersensitivity/allergic reaction).

Substantial Amendment 2: 10 Jan 2022

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The protocol was mainly amended to incorporate and implement changes for statistical analysis, consistency with supporting study documents and suggestions made based on Investigator experiences.

Changes in inclusion/exclusion and discontinuation criteria:

• Updated exclusion criterion for participants with inadequate renal and hepatic function to specify exception for participants with Gilbert's syndrome.

• Added antioestrogens, aromatase inhibitors, low molecular weight heparins, vitamin K, vitamin K antagonists (eg, warfarin, acenocumarol), emtricitabine, tenofovir, adefovir as prohibited medication and pregabalin as not prohibited medication.

• Added pregnancy and breastfeeding as exclusion criteria and breastfeeding under discontinuation/withdrawal criteria.

• Amended text to specify hepatitis B exclusion criteria.

Substantial Amendment 3: 19 Jan 2023

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The protocol was mainly amended to incorporate and implement 10% increase in the number of participants to be enrolled for the Transition Period to meet the requirements of US-FDA, considering the drop-out was higher than expected.

Non-Substantial Amendment 2 (28 Mar 2023)

This amendment was considered to be non-substantial because it neither significantly impacted the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The protocol was mainly amended to incorporate and implement responses and suggestions made by the US-FDA to Sections Estimands and Handling of Missing Data.

Baseline data

Demographics

Table 24: Subject Demographics - Main Period (Full Analysis Set for Main Period)

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Age (years)	n	242	231	473
	Mean	66.7	66.8	66.7
	SD	5.20	4.91	5.06
	Median	66.0	66.0	66.0
	Minimum	60	60	60
	Maximum	83	84	84
Gender				
Female	n (%)	242 (100)	231 (100)	473 (100)
Osteoporosis diagnosis				

Subjects with prior osteoporosis diagnosis	n (%)	188 (77.7)	163 (70.6)	351 (74.2)
Subjects with new osteoporosis diagnosis	n (%)	54 (22.3)	68 (29.4)	122 (25.8)
Ethnic Origin				
Hispanic or Latino	n (%)	18 (7.4)	22 (9.5)	40 (8.5)
Not Hispanic or Latino	n (%)	223 (92.1)	209 (90.5)	432 (91.3)
Not Reported	n (%)	1 (0.4)	0	1 (0.2)
Race				
White	n (%)	241 (99.6)	229 (99.1)	470 (99.4)
Black or African American	n (%)	0	2 (0.9)	2 (0.4)
Native Hawaiian or Other Pacific Islander	n (%)	1 (0.4)	0	1 (0.2)
Height (cm)	n	242	231	473
	Mean	159.153	159.278	159.214
	SD	5.8416	6.6719	6.2545
	Median	159.000	160.000	159.000
	Minimum	143.50	139.00	139.00
	Maximum	179.80	176.70	179.80
Weight (kg)	n	242	231	473
	Mean	63.99	65.05	64.51
	SD	9.695	8.953	9.345
	Median	63.00	64.50	64.00
	Minimum	50.0	50.0	50.0
	Maximum	90.0	89.7	90.0
BMI (kg/m^2)	n	242	231	473
	Mean	25.249	25.714	25.476
	SD	3.4772	3.7615	3.6225
	Median	24.795	25.390	25.070

	Minimum	18.07	18.42	18.07
	Maximum	36.46	37.80	37.80
Country				
United States of America	n (%)	11 (4.5)	9 (3.9)	20 (4.2)
Spain	n (%)	13 (5.4)	22 (9.5)	35 (7.4)
Bulgaria	n (%)	40 (16.5)	27 (11.7)	67 (14.2)
Hungary	n (%)	19 (7.9)	20 (8.7)	39 (8.2)
Ukraine	n (%)	1 (0.4)	2 (0.9)	3 (0.6)
Italy	n (%)	8 (3.3)	15 (6.5)	23 (4.9)
Czechia	n (%)	25 (10.3)	36 (15.6)	61 (12.9)
Poland	n (%)	125 (51.7)	100 (43.3)	225 (47.6)

Abbreviations: BMI = body mass index; N = number of subjects in the analysis set; n = number of subjects in the specific category; SD = standard deviation.

%: calculated using the number of subjects in the analysis set as the denominator (n/N*100).

Source: Table 14.1.3.1

Baseline Disease Characteristics

The Summary of baseline absolute BMD as measured by DXA during the Screening Period for lumbar spine (LS), total hip (TH), femoral neck (FN) for the FAS are presented in the tables below. Summary measurements are also available for the PPS.

Table 25: Study RGB-14-101: Summary of Lumbar Spine, Femoral Neck and Total Hip Baseline Bone Mineral Density (g/cm2)- Main period (Full Analysis Set for Main Period)

Parameter	stat	Overall	Prolia	RGB-14-P
Femoral Neck - IQC and XCAL Corrected BMD (g/cm^2)	n	473	231	242
	Mean	0.7088858	0.7112641	0.7066157
	SD	0.1031359	0.110245	0.0960356
	Median	0.708	0.711	0.706
	Min	0.459	0.459	0.498
	Max	1.012	1.011	1.012
Total Hip - IQC and XCAL Corrected BMD (g/cm^2)	n	473	231	242
	Mean	0.7721966	0.7734719	0.7709793
	SD	0.0909062	0.0963123	0.0856111
	Median	0.773	0.775	0.773
	Min	0.525	0.525	0.556
	Max	1.049	1.049	1.031
Lumbar Spine - IQC and XCAL Corrected BMD (g/cm^2)	n	473	231	242
	Mean	0.7769958	0.7771039	0.7768926
	SD	0.0665795	0.0657667	0.0674823
	Median	0.776	0.772	0.782
	Min	0.581	0.581	0.617
	Max	0.92	0.897	0.92

n: number of subjects included in the analysis set for each treatment and overall; SD: standard deviation

Table 26: Study RGB-14-101: Summary of Lumbar Spine, Femoral Neck and Total Hip Baseline T-score (g/cm2)- Main period (Full Analysis Set for Main Period)

Parameter	Stat	RGB-14-P (N=242)	Prolia (N=231)	Overall (N=473)
Femoral Neck - IQC and XCAL Corrected BMD T-Score	n (%)	242 (100)	231 (100)	473 (100)
	Mean	-2.08	-2.05	-2.07
	SD	0.64	0.74	0.69
	Median	-2.10	-2.10	-2.10
	Minimum	-3.70	-3.80	-3.80
	Maximum	0.10	0.10	0.10
Total Hip - IQC and XCAL Corrected BMD T-Score	n (%)	242 (100)	231 (100)	473 (100)
	Mean	-1.80	-1.78	-1.79
	SD	0.72	0.79	0.75
	Median	-1.80	-1.80	-1.80
	Minimum	-3.80	-3.90	-3.90
	Maximum	0.20	0.30	0.30
Lumbar Spine - IQC and XCAL Corrected BMD T-Score	n (%)	242 (100)	231 (100)	473 (100)
	Mean	-3.06	-3.05	-3.06
	SD	0.40	0.43	0.41
	Median	-3.00	-2.90	-3.00
	Minimum	-4.10*	-4.10	-4.10
	Maximum	-2.20	-2.30	-2.20

*n: number of subjects included in the analysis set for each treatment and overall; SD: standard deviation. *: patients [redacted], [redacted], [redacted] had IQC and XCAL corrected T-score values of -4.1. Their uncorrected T-score values were -4.0, thus they were eligible to participate in the study.*

Table 27: Study RGB-14-101: Summary of baseline serum P1NP and sCTX levels - Main period (Pharmacodynamics Analysis Set for Main Period)

Parameter	stat	Overall	Prolia	RGB-14-P
Procollagen 1 N-Terminal Propeptide (ng/mL)	n	468	228	240
	Mean	61.098291	61.364035	60.845833
	SD	23.246056	23.849396	22.705084
	Median	59.4	59.8	59.3
	Min	12	12	13.9
	Max	159	159	156
Type I Collagen C-Telopeptides (ng/mL)	n	468	228	240
	Mean	0.5087308	0.5054912	0.5118083
	SD	0.2183937	0.2183011	0.2188933
	Median	0.487	0.4905	0.486
	Min	0.056	0.056	0.099
	Max	1.29	1.29	1.24

n: number of subjects included in the analysis set for each treatment and overall; SD: standard deviation

Table 28: Summary of Lumbar Spine Bone Mineral Density by visit – Full Analysis Set for Main Period

Table 14.2.1.1.1 Summary of Lumbar Spine Bone Mineral Density (g/cm2) by visit - Main period (Full Analysis Set for Main Period)

Nominal Time Point	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Pre-dose Baseline				
Result	n (%)	242 (100)	231 (100)	473 (100)
	Mean	0.7769	0.7771	0.7770
	SD	0.0675	0.0658	0.0666
	95% CI	0.7683 , 0.7854	0.7686 , 0.7856	0.7710 , 0.7830
	Median	0.7820	0.7720	0.7760
	Minimum	0.617	0.581	0.581
	Maximum	0.920	0.897	0.920

CfB: Change from Baseline; %CfB:[(value-baseline)/baseline]*100; CI: Confidence Interval; N: The number of subjects included in the analysis set for each treatment and overall; SD: standard deviation.
In this table, BMD is summarised without missing data imputation.
Bone Mineral Density (BMD) presented in this table is corrected for instrument quality control (IQC) and cross calibration (Xcal).

Reference Listing: 16.2.6.1

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Table 29: Summary of Total Hip Bone Mineral Density by visit – Full Analysis Set for Main Period

Table 14.2.5.1 Summary of Total Hip Bone Mineral Density (g/cm2) by visit - Main period (Full Analysis Set for Main Period)

Nominal Time Point	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Pre-dose Baseline				
Result	n (%)	242 (100)	231 (100)	473 (100)
	Mean	0.7710	0.7735	0.7722
	SD	0.0856	0.0963	0.0909
	95% CI	0.7601 ; 0.7818	0.7610 ; 0.7860	0.7640 ; 0.7804
	Median	0.7730	0.7750	0.7730
	Minimum	0.556	0.525	0.525
	Maximum	1.031	1.049	1.049

CfB: Change from Baseline; %CfB:[(value-baseline)/baseline]*100; CI: Confidence Interval; N: The number of subjects included in the analysis set for each treatment and overall; SD: standard deviation.
In this table, BMD is summarised without missing data imputation.
Bone Mineral Density (BMD) presented in this table is corrected for instrument quality control (IQC) and cross calibration (Xcal).

Reference Listing: 16.2.6.1

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Table 30: Summary of Femoral Neck Bone Mineral Density by visit – Full Analysis Set for Main Period

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Main period (Week 52) analysis Page 1 of 4
Main period dataset Data version: 13-Dec-2023
Table 14.2.6.1 Summary of Femoral Neck Bone Mineral Density (g/cm2) by visit - Main period (Full Analysis Set for Main Period)

Nominal Time Point	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Pre-dose Baseline				
Result	n (%)	242 (100)	231 (100)	473 (100)
	Mean	0.7066	0.7113	0.7089
	SD	0.0960	0.1102	0.1031
	95% CI	0.6945 ; 0.7188	0.6970 ; 0.7256	0.6996 ; 0.7182
	Median	0.7060	0.7110	0.7080
	Minimum	0.498	0.459	0.459
	Maximum	1.012	1.011	1.012

Table 31: Summary of sCTX results by visit - Pharmacodynamic Analysis Set for Main Period

Gedeon Richter Plc. RGB-14-101
Main period (Week 52) analysis Page 1 of 14
Main period dataset Data version: 13-Dec-2023
Table 14.2.9.1 Summary of sCTX results by visit - Main period (Pharmacodynamic Analysis Set for Main Period)

Nominal Time Point	Statistic	RGB-14-P (N = 241)	Prolia (N = 229)	Overall Study (N = 470)
Pre-dose Baseline				
Result	n (%)	240 (99.6)	228 (99.6)	468 (99.6)
	Mean	0.5118	0.5055	0.5087
	SD	0.2189	0.2183	0.2184
	Median	0.4860	0.4905	0.4870
	Minimum	0.099	0.056	0.056
	Maximum	1.240	1.290	1.290

CfB: Change from Baseline, as reduction from baseline. %CfB: [(baseline - value)/baseline] *100; N: The number of subjects included in the analysis set for each treatment and overall; SD: standard deviation. In this table, below the limit of quantification (BLQ) values are imputed as the lower limit of quantification (LLOQ) itself.
In some instances, results were received with two test codes for sCTX (received as ZCTXG and ZCTX1); in these instances, based on instructions received from laboratory, the results received under code ZCTXG was considered as latest and used in this table.

Reference Listing: 16.2.6.6

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Table 32: Summary of P1NP results by visit - Pharmacodynamic Analysis Set for Main Period

Gedeon Richter Plc. RGB-14-101
Main period (Week 52) analysis Page 1 of 5
Main period dataset Data version: 13-Dec-2023
Table 14.2.12.1 Summary of P1NP results by visit - Main period (Pharmacodynamic Analysis Set for Main Period)

Nominal Time Point	Statistic	RGB-14-P (N = 241)	Prolia (N = 229)	Overall Study (N = 470)
Pre-dose Baseline				
Result	n (%)	240 (99.6)	228 (99.6)	468 (99.6)
	Mean	60.85	61.36	61.10
	SD	22.705	23.849	23.246
	Median	59.30	59.80	59.40
	Minimum	13.9	12.0	12.0
	Maximum	156.0	159.0	159.0

CfB: Change from Baseline, as reduction from baseline. %CfB: [(baseline - value)/baseline] *100; N: The number of subjects included in the analysis set for each treatment and overall; SD: standard deviation. In this table, below the limit of quantification (BLQ) values are imputed as the lower limit of quantification (LLOQ) itself.
In some instances, results were received with two test codes for P1NP (received as ZP1NG and ZP1NB); in these instances, based on instructions received from laboratory, the results received under code ZP1NG was considered as latest and used in this table.

Reference Listing: 16.2.6.6

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Table 33: Study RGB-14-101: Summary of fractures by anatomical sites (i.e. vertebral, non-vertebral) and traumatic fractures based on the patients' medical history (Enrolled Analysis Set)

Variable	Stat	RGB-14-P (N=242)	Prolia (N=231)	Overall (N=473)
Vertebral fractures	n (%) [events]	5 (2.07) [5]	4 (1.73) [6]	9 (1.90) [11]
Nonvertebral fractures	n (%) [events]	70 (28.9) [115]	57 (24.7) [90]	127 (26.8) [205]
Traumatic fractures	n (%) [events]	2 (0.83) [3]	6 (2.60) [7]	8 (1.69) [10]

N = number of subjects included in the analysis set for each treatment and overall; n = The number of subjects in specific category.

Table 34: Study RGB-14-101: Summary of fractures within one and two years of screening based on the patients' medical history (Full Analysis Set)

	Within 1 year		Within 2 years	
	RGB-14-P N=242	Prolia N=231	RGB-14-P N=242	Prolia N=231
Number of subjects who had any fractures [n (%) (events)]	23 (9.50) 27	16 (6.93) 23	25 (10.3) 31	23 (9.96) 35

Imputation of incomplete Medical History start date:
Missing day only: the last day of the month is assigned to the missing day.
Missing month and day: the last month and day of the year is assigned to the missing month and day.
Events with completely missing start date are considered to have occurred within 1 year of the screening date.
In total there were 4 completely missing MH date in 4 subjects, none of them was 'Fracture'.
Contains all Dictionary Derived Term, which contains the 'Fracture' term, excluding traumatic fractures.

Table 35: Study RGB-14-101: Summary patients of experienced hypersensitivity from their medical history (Full Analysis Set)

Stat	RGB-14-P (N=242)	Prolia (N=231)	Overall (N=473)
n	12	10	22
Percent	5.19	4.13	4.65
n event	18	13	31

Table 36: Study RGB-14-101: Summary of prior bisphosphonate use (Full Analysis Set)

Stat	RGB-14-P (N=242)	Prolia (N=231)	Overall (N=473)
Prior Bisphosphonate use			
n	17	18	35
Percent	7.02	7.79	7.40
Prior Bisphosphonate use duration (in months)			
n	21*	18	39
SD	20.30	10.29	16.31
Min	0.00**	7.00	0.00
Median	10.00	14.50	12.00
Mean	16.71	19.28	17.90
Max	72.00	36.00	72.00

**: patients in the RGB-14-P Treatment group [redacted], [redacted], [redacted] and [redacted] have started bisphosphonates on multiple occasions.*
***: patients [redacted] and [redacted] only the year was given for start and end date.*

Table 37: Study RGB-14-101: Summary of 25-Hydroxyvitamin D3 levels at baseline (Full Analysis Set)

Stat	RGB-14-P (N=242)	Prolia (N=231)	Overall (N=473)
n	242	231	473
Mean	96.45	91.71	94.14
SD	34.91	35.55	35.26
Median	89.00	83.00	86.00
Min	47.00	27.00	27.00
Max	329.0	310.0	329.0

Medical History and Concurrent Illnesses

A summary of medical and surgical history for the FAS for the Main Period is provided in the table below. The most frequently reported medical history by SOC (in ≥ 20% participants overall) included social circumstances (100%), musculoskeletal and connective tissue disorders (82.2%), metabolism and nutrition disorders (59%), surgical and medical procedures (58.6%), vascular disorders (52.4%), injury, poisoning and procedural complications (31.7%), endocrine disorders (27.3%), gastrointestinal disorders (25.8%), and infections and infestations (25.4%). The medical and surgical history reported were comparable between the RGB-14-P and Prolia treatment groups.

The most frequently reported concomitant illnesses by SOC (in ≥ 20% participants overall) included social circumstances (99.2%), musculoskeletal and connective tissue disorders (81.4%), metabolism and nutrition disorders (57.7%), vascular disorders (51%), endocrine disorders (24.9%), and gastrointestinal disorders (21.1%). The concomitant illness reported was comparable between the RGB-14-P and Prolia treatment groups.

Table 38: Summary of Medical and Surgical History - Main Period (Full Analysis Set for Main Period)

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Main period (Week 52) analysis Page 1 of 61
Main period dataset Data version: 13-Dec-2023
Table 14.1.6.1.1 Summary of Medical and Surgical History - Main period (Full Analysis Set for Main Period)

System Organ Class Preferred Term	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Social circumstances	n (%)	242 (100)	231 (100)	473 (100)
Menopause	n (%)	163 (67.4)	159 (68.8)	322 (68.1)
Postmenopause	n (%)	82 (33.9)	73 (31.6)	155 (32.8)
Joint prosthesis user	n (%)	1 (0.4)	0	1 (0.2)
Organ donor	n (%)	1 (0.4)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	n (%)	205 (84.7)	184 (79.7)	389 (82.2)
Osteoporosis	n (%)	151 (62.4)	124 (53.7)	275 (58.1)
Osteoarthritis	n (%)	43 (17.8)	39 (16.9)	82 (17.3)
Spinal osteoarthritis	n (%)	49 (20.2)	32 (13.9)	81 (17.1)
Osteoporosis postmenopausal	n (%)	37 (15.3)	39 (16.9)	76 (16.1)

Prior and Concomitant Treatments

The most frequently reported concomitant medications (in ≥ 10% participants overall) included calperos osteo (23.7%), calperos (calcium carbonate) (21.8%), calcium (20.7%), vigantol (colecalciferol) (16.9%), vigantoletten, and vitamin D3 (both 11%). The additional frequently reported concomitant medications by ATC level 4 term (in ≥ 10% participants overall) included 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (38.5%), beta blocking agents, selective (27.1%), thyroid hormones (19%), ACE inhibitors, plain (18%), anilides (15%), dihydropyridine derivatives (13.3%), proton pump inhibitors (13.1%), angiotensin II receptor blockers, plain (12.3%), platelet aggregation inhibitors excl. heparin and COVID-19 vaccines (both 10.1%). The concomitant medications reported were comparable between the RGB-14-P and Prolia treatment groups.

The reported concomitant procedures by SOC included investigations (10.6%) and surgical and medical procedures (8.7%).

Numbers analysed

Analysis Set

Full Analysis Set (FAS) and Safety Analysis Set (SAF): 242 patients treated with RGB-14-P and 231 patients treated with the RP (Total 473 patients). None of the patients were excluded from the FAS or SAF for having received no study intervention, therefore both sets comprised 473 patients.

In the FAS, two intercurrent events (ICEs) were observed: ICE1: The first and/or the second dose of randomised IMP is not administered. ICE2: The participant received other medication (listed as prohibited therapy in the clinical study protocol) alongside the IMP, which affects the primary variable.

Per Protocol Set (PPS): 240 patients treated with RGB-14-P and 229 patients treated with the RP (Total 469 patients). The major deviations that led to exclusion from the PPS were related to meeting an exclusion criterion in 3 participants and 'other' criteria (involved in another study) in 1 participant.

Pharmacodynamic Analysis Set (PDS): 241 patients treated with RGB-14-P and 229 patients treated with the RP (Total 470 patients).

Immunogenicity Analysis Set: 239 patients treated with RGB-14-P and 228 patients treated with the RP (Total 467 patients).

The selection of randomised patients was based on an extensive screening period: 1211 postmenopausal women were enrolled, of these 738 postmenopausal women were screen failures. Main reasons for screen failure were:

• Participant has a current uncontrolled status of hypothyroidism (94)

• Patient withdrew her consent (86)

• Participant has an active infection, including, but not limited to SARS-CoV-2, hepatis B, hepatitis C and human immunodeficiency virus infections during the Screening Period. (78)

• Participant had BMD with T-score >-2.5 OR < -4.0 at the lumbar spine (69)

Statistical analysis: Safety assessments included collection of AEs, serious AEs (SAEs), vital signs, physical examination, electrocardiograms (ECGs), laboratory assessments, concomitant medications, injection site reaction and fracture assessment. Continuous data were summarised in terms of the mean, SD, median, minimum, maximum, quartiles and number of observations. Categorical data were summarised in terms of the number of participants providing data at the relevant time point (n), frequency counts and percentages.

Outcomes and estimation

Primary efficacy endpoint

The primary efficacy endpoint was the %CfB in lumbar spine BMD at Week 52. The sensitivity analysis and supplemental analysis were performed for %CfB in lumbar spine BMD at Week 52.

Analysis Based on EMA Scientific Advice

Missing data without experiencing ICE2 were assumed to be MCAR and were not imputed. Post-ICE2, data was artificially set as missing and were assumed to be MAR in the Prolia treatment group (i.e., assumed to have behaved like participants in the same group had they not taken prohibited medication). However, data after ICE2 in the RGB-14-P treatment group were artificially set as missing were assumed to be MNAR and imputed under the null hypothesis (i.e., assumed to worsen from MAR by an amount of the equivalence margin [delta = -1.45]).

Table 39: Analysis of Lumbar Spine BMD at Week 52 - Primary Treatment Policy Estimand - EMA Submission (Full Analysis Set for Main Period)

Primary TPE - Regular missing data MCAR - Post-ICE2 assessments Prolia: MAR, RGB-14-P: MNAR

		Comparison between Study Treatment Groups	
Study Treatment	**Adjusted Means (95% CI)**	**Estimated Difference (95% CI)**	**Equiv. Claim**
RGB-14-P (N = 242)	4.89 (3.547, 6.235)	0.34 (-0.402, 1.090)	Met
Prolia (N = 231)	4.55 (3.220, 5.874)		

Primary TPE - Regular missing data MCAR - Post-ICE2 assessments Prolia: MAR, RGB-14-P: MNAR

		Comparison between Study Treatment Groups	
Study Treatment	**Adjusted Means (95% CI)**	**Estimated Difference (95% CI)**	**Equiv. Claim**

Abbreviations: ANCOVA = analysis of covariance; BMD = bone mineral density; CI = confidence interval; EMA = European Medicines Agency; Equiv. = equivalence; IMP = investigational medicinal product; IQC = instrument quality control; MAR = missing at random; MCAR = missing completely at random; MNAR = missing non at random; N = number of subjects in the analysis set; SAP = Statistical Analysis Plan; TPE = treatment policy estimand; US = United States; Xcal = cross calibration; % CfB = percent change from baseline.

ICE2: Intercurrent Event 2. The participant received other medication alongside the IMP, which affects the primary variable (Appendix 16.1.1, Section 6.5.1).

The analysis was performed with an ANCOVA model with %CfB in lumbar spine BMD at Week 52 as the dependent variable; covariates are treatment arm (RGB-14-P and US-licensed Prolia), stratification factors at randomisation (previous use of bisphosphonates [yes/no] and geographical region [Europe, US]), baseline BMD value in lumbar spine, machine type and machine type*baseline BMD value interaction. Estimated difference: RGB-14-P - Prolia.

Multiple imputation procedures are described in the SAP, Version 1.0 (Appendix 16.1.9).

BMD analysed in this table is corrected for IQC and Xcal.

Missing values are assumed to be MCAR and are not imputed, post-ICE2 assessments are imputed under null hypothesis. Equivalence claimed if the estimated difference lower limit (left-side) of the two-sided 95% CI will be greater than -1.45 and the upper limit (right side) will be lower than 1.45; details in the SAP, Version 1.0.

Source: Table 14.2.3.3

Table 40: Summary of Lumbar Spine BMD by visit - Main Period (Full Analysis Set for Main Period)

Gedeon Richter Plc. RGB-14-101
Main period (Week 52) analysis Page 4 of 4
Main period dataset Data version: 13-Dec-2023
Table 14.2.1.1.1 Summary of Lumbar Spine Bone Mineral Density (g/cm2) by visit - Main period (Full Analysis Set for Main Period)

Nominal Time Point	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
TP2 Day 183 - Week 52				
%CfB	n (%)	222 (91.7)	206 (89.2)	428 (90.5)
	Mean	5.68	5.19	5.44
	SD	3.535	4.118	3.830
	95% CI	5.21 , 6.14	4.62 , 5.75	5.08 , 5.81
	Median	5.56	4.83	5.31
	Minimum	-5.6	-9.7	-9.7
	Maximum	15.9	24.0	24.0

CfB: Change from Baseline; %CfB:[(value-baseline)/baseline]*100; CI: Confidence Interval; N: The number of subjects included in the analysis set for each treatment and overall; SD: standard deviation.
In this table, BMD is summarised without missing data imputation.
Bone Mineral Density (BMD) presented in this table is corrected for instrument quality control (IQC) and cross calibration (Xcal).

Reference Listing: 16.2.6.1

/unblinded/gedeo252679/stats/interim_main/prog/tables/t_admk_lsbmd_sum.sas/15APR2024 11:13

Table 41: Summary of missing Lumbar Spine BMD - Main Period (Full Analysis Set for Main Period)

Gedeon Richter Plc. RGB-14-101
Main period (Week 52) analysis Page 1 of 1
Main period dataset Data version: 13-Dec-2023
Table 14.2.2.1.1 Summary of missing Lumbar Spine Bone Mineral Density (g/cm2) - Main period (Full Analysis Set for Main Period)

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Subjects with available baseline and week 52	n (%)	222 (91.7)	206 (89.2)	428 (90.5)
Subjects with available baseline and missing week 52	n (%)	20 (8.3)	25 (10.8)	45 (9.5)
Subjects with missing baseline	n (%)	0	0	0

Table 42: Summary of missing Lumbar Spine BMD - Main Period (per Protocol Analysis Set for Main Period)

Gedeon Richter Plc. RGB-14-101
Main period (Week 52) analysis Page 1 of 1
Main period dataset Data version: 13-Dec-2023
Table 14.2.2.1.2 Summary of missing Lumbar Spine Bone Mineral Density (g/cm2) - Main period (Per Protocol Analysis Set for Main Period)

Characteristic	Statistic	RGB-14-P (N = 240)	Prolia (N = 229)	Overall Study (N = 469)
Subjects with available baseline and week 52	n (%)	222 (92.5)	205 (89.5)	427 (91.0)
Subjects with available baseline and missing week 52	n (%)	18 (7.5)	24 (10.5)	42 (9.0)
Subjects with missing baseline	n (%)	0	0	0

Sensitivity Analysis

To challenge the robustness of the primary endpoint a sensitivity analysis was performed. Missing data post baseline were imputed as a sensitivity estimation. Missing data ware assumed to be MAR. Under the Prolia treatment group, data artificially set as missing after ICE2 occurrence was assumed to be MAR (ie, data was imputed assuming they would have behaved like participants in the same group had they not have an ICE2). However, under the RGB-14-P treatment group data artificially set as missing after ICE2 occurrence was imputed using MNAR and imputed under the null hypothesis (ie, after ICE2 missing data were assumed to worsen from MAR by an amount of equivalence margin [delta = -1.45]).

Table 43: Analysis of Lumbar Spine BMD at Week 52 - Primary Treatment Policy Estimand - EMA Submission - Sensitivity (Full Analysis Set for Main Period)

Sensitivity TPE – Regular missing data MAR – Post-ICE2 assessments Prolia: MAR, RGB-14-P: MNAR

		Comparison between Study Treatment Groups	
Study Treatment	**Adjusted Means (95% CI)**	**Estimated Difference (95% CI)**	**Equiv. Claim**
RGB-14-P (N = 242)	4.93 (3.657, 6.197)	0.30 (-0.472, 1.062)	Met
Prolia (N = 231)	4.63 (3.362, 5.901)		

Abbreviations: ANCOVA = analysis of covariance; BMD = bone mineral density; CI = confidence interval; EMA = European Medicines Agency; Equiv = equivalence; FCS = fully conditional specification; IMP = investigational medicinal product; IQC = instrument quality control; MAR = missing at random; MNAR = missing non at random; N = number of subjects in the analysis set; SAP = Statistical Analysis Plan; TPE = treatment policy estimand; US = United States; Xcal = cross calibration; %CfB = percent change from baseline.

ICE2: Intercurrent Event 2. The participant received other medication alongside the IMP, which affects the primary variable (Appendix 16.1.1, Section 6.5.1).

The analysis was performed with an ANCOVA model with %CfB in lumbar spine BMD at Week 52 as the dependent variable; covariates are treatment arm (RGB-14-P and US-licensed Prolia), stratification factors at randomisation (previous use of bisphosphonates [yes/no] and geographical region [Europe, US]), Baseline BMD value in lumbar spine, machine type and machine type*baseline BMD value interaction. Estimated difference: RGB-14-P – Prolia.

Multiple imputation procedures are described in the SAP, Version 1.0 (Appendix 16.1.9).

BMD analysed in this table is corrected for IQC and Xcal.

Missing values (originally or post-ICE2 assessments) are imputed using FCS method where variables from primary efficacy ANCOVA model are used to impute missing values via SAS PROC MI, details in the SAP, Version 1.0.

Source: Table 14.2.4.1

Supplemental Analysis

Table 44: Analysis of Lumbar Spine BMD - Supplementary Robustness Analysis - MMRM (Full Analysis Set for Main Period)

Gedeon Richter Plc. RGB-14-101
Main period (Week 52) analysis Page 1 of 1
Main period dataset Data version: 13-Dec-2023
Table 14.2.4.5 Analysis of Lumbar Spine Bone Mineral Density (g/cm2) - Supplemental Robustness Analysis - Mixed model repeated measures (Full Analysis Set for Main Period)

Supplementary efficacy analysis - Regular missing data MCAR - Post-ICE assessments excluded from analysis

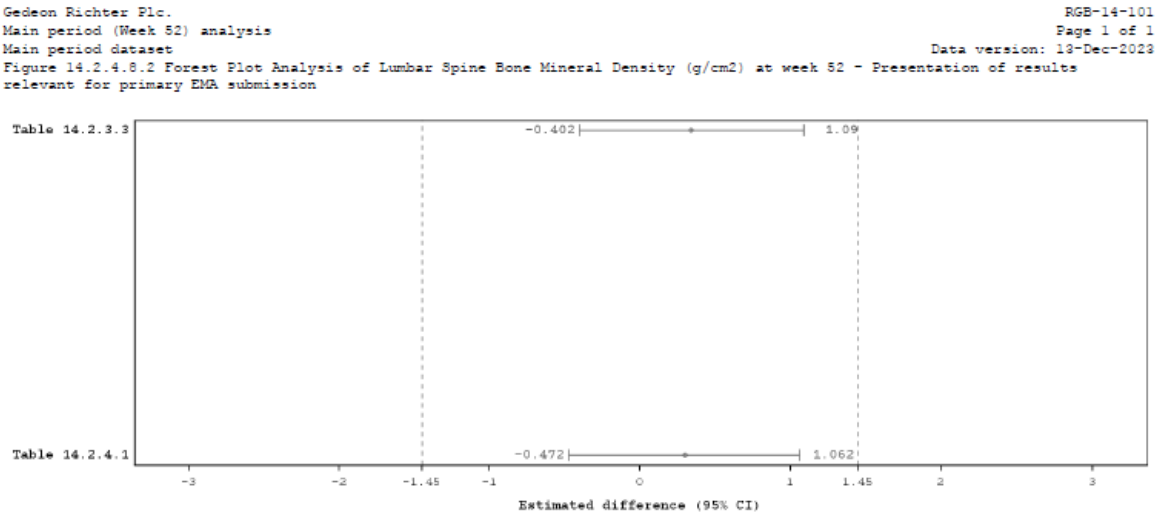
			Comparison between Study Treatment Groups	
Time point	Study Treatment	Adjusted means (95% CI)	Estimated difference (95% CI)	P-value
TP2 Day 1 - Week 26	RGB-14-P (n=221)	2.46 (1.280 , 3.640)	0.08 (-0.663 , 0.824)	0.832
	Prolia (n=211)	2.38 (1.216 , 3.543)		
TP2 Day 183 - Week 52	RGB-14-P (n=213)	4.65 (3.470 , 5.824)	0.36 (-0.373 , 1.093)	0.335
	Prolia (n=194)	4.29 (3.123 , 5.450)		

CfB: Change from Baseline; CI: Confidence Interval; MCAR: Missing Completely At Random; TP: Treatment Period.
ICE1: Intercurrent Event 1 The first and/or the second dose of randomised IMP is not administered.
ICE2: Intercurrent Event 2 The participant received other medication alongside the IMP, which affects the primary variable (please refer to protocol section [Prohibited Therapy]).
Bone Mineral Density (BMD) analysed in this table is corrected for instrument quality control (IQC) and cross calibration (Xcal).
The analysis is performed with a mixed model repeated measures with observed %CfB in lumbar spine BMD as the dependent variable; covariates are treatment arm (RGB-14-P and US licenced Prolia), stratification factors at randomization (Previous use of bisphosphonates [yes/no] and geographical region [Europe, US], Baseline BMD value in lumbar spine, machine type and machine type*baseline BMD value interaction, study week and study week*treatment arm interaction.

Reference Listing: 16.2.6.1

/unblinded/gedeo252679/stats/interim_main/prog/tables/t_admk_lsbmd_supple.sas/15APR2024 11:13

Table 45: Forest Plot Analysis of lumbar Spine BMD at Week 52



Analysis Based on USFDA Scientific Advice

The non-inferiority and the no-superiority assessments were performed with an ANCOVA model with %CfB in lumbar spine BMD at Week 52 as the dependent variable. Covariates for boths assessments were treatment Arm (RGB 14 P and US-licensed Prolia), stratification factors at randomization (previous use of bisphosphonates [yes/no] and geographical region [Europe, US]), baseline BMD value in lumbar spine, machine type and machine type*baseline BMD value interaction. The estimated difference is RGB-14-P - Prolia.

Data observed after the occurrence of ICE2 were artificially set as missing. Participants in the Prolia treatment group with missing values (originally or post-ICE2) were assumed to be MAR (ie, assumed to have behaved like participants in the same group had they not have a missing value or have an ICE2). The participants in the RGB-14-P treatment group with missing values (originally or post-ICE2) were assumed to be MNAR and imputed under the null hypothesis (ie, missing data were assumed to worsen from "MAR" by an amount of equivalence margin [delta = -1.45 when testing for non-inferiority and delta=1.45 when testing for non-superiority]).

Compared with the baseline, an increase was observed in the lumber spine BMD up to Week 52 in both treatment groups. At Week 52, the mean (SD) %CfB was 5.68 (3.535) in the RGB-14-P group and 5.19 (4.118) in the Prolia group.

The estimated difference for the non-inferiority test between the two treatment groups was 0.18 (90% CI = -0.465, 0.825).

The estimated difference for the non-superiority test between the two treatment groups was 0.55 (90% CI = -0.099, 1.191).

Tipping point analysis

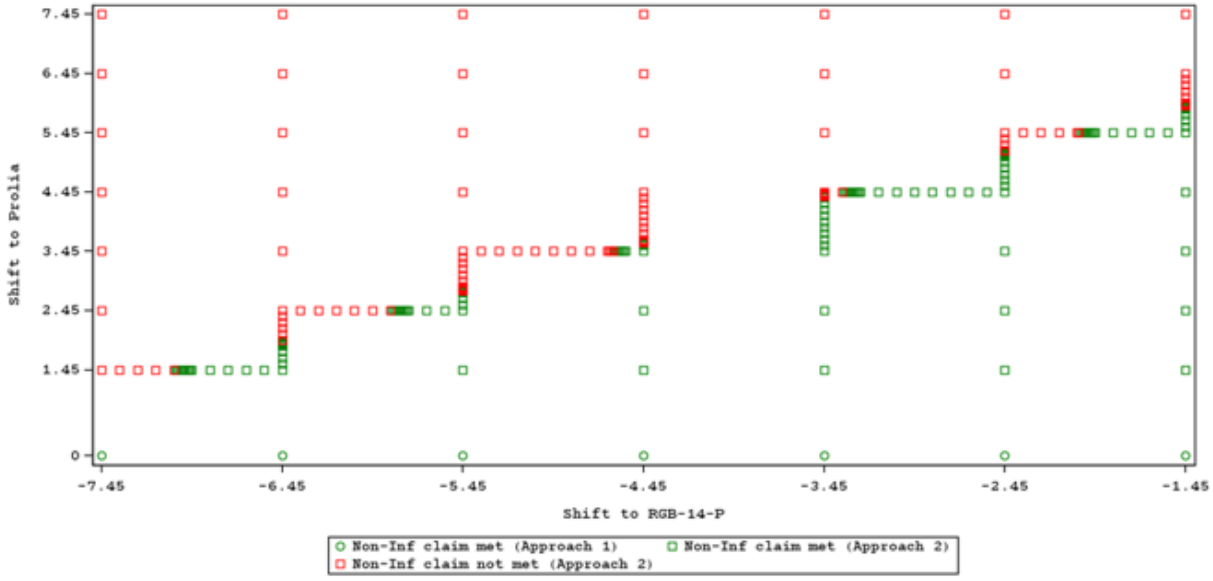
A Tipping Point Analysis is a method of exploring the influence of missingness on the overall conclusion of the treatment difference by shifting imputed missing values in the test group towards the reference group until the study results are reversed. Clinical judgement was also applied to the plausibility of the tipping point (delta adjustment).

The tipping point analysis was executed following two approaches.

• Approach 1: The data in the Prolia treatment group were assumed to be MAR (ie, shift in delta of 0), however data in the RGB-14-P treatment group after ICE2 were assumed to be MNAR and applying shifts ranging from 'delta' (-1.45 when testing non-inferiority, 1.45 when testing non-superiority) to approximately 5 times delta (-7.45 when testing non-inferiority, 7.45 when testing non-superiority).

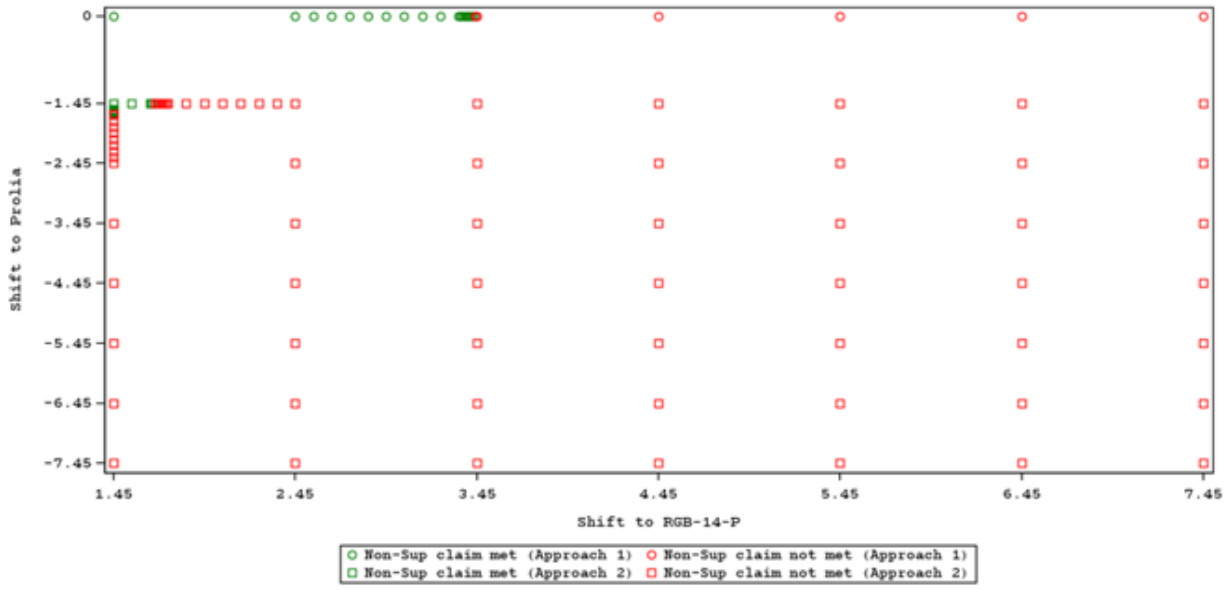
• Approach 2: The MNAR shifts were applied to both the Prolia and RGB-14-P treatment groups. When testing non-inferiority, shifts in the range from 1.45 to 7.45 were applied to Prolia while shifts in the range from -7.45 to -1.45 were applied to RGB-14-P. When testing non-superiority, shifts in the range from -7.45 to -1.45 were applied to Prolia while shifts in the range from 1.45 to 7.45 were applied to RGB-14-P.

Figure 12: Analysis of Lumbar Spine Bone Mineral Density (g/cm2) at week 52 - Primary Treatment Policy Estimand - FDA submission - Sensitivity two-dimensional tipping point multiple imputation - non inferiority (Full Analysis Set for Main Period



Result:
Approach 1: For all shifts of RGB-14-P, the non-inferiority claim is maintained.
Approach 2: For a shift of +1.45 for Prolia, non-inferiority claim is maintained even for a shift of –7.03 for RGB-14-P. For a shift of -1.45 for RGB-14-P, non-inferiority claim is maintained even for a shift of +5.88 for Prolia.

Figure 13: Analysis of Lumbar Spine Bone Mineral Density (g/cm2) at week 52 - Primary Treatment Policy Estimand - FDA submission - Sensitivity two-dimensional tipping point multiple imputation - non superiority (Full Analysis Set for Main Period)



Result:
Approach 1: For shifts of RGB-14-P of +3.43 the claim of non-superiority is maintained. This is more than double the equivalence margin.
Approach 2: For a shift of -1.45 for Prolia, non-superiority claim is maintained even for a shift of +1.67 for RGB-14-P. For a shift of +1.45 for RGB-14-P, non-superiority claim is maintained even for a shift of –1.63 for Prolia.

Secondary Estimand

A secondary estimand was applied to additionally challenge the robustness of the primary analyses.

Table 46: Analysis of Lumbar Spine BMD at Week 52 - Secondary Stratum Estimand (PPS for Main Period)

Secondary PSE - PPS, completer, not having experienced any of the two ICEs

		Comparison between Study Treatment Groups			
Study Treatment	Adjusted Means (95% CI)	Estimated Difference (95% CI)	Non-Inf. P-value	Non-Sup. P-value	Equiv. Claim
RGB-14-P (N = 216)	4.88 (3.539, 6.212)	0.48 (-0.268, 1.227)	<0.001	0.005	Met
Prolia (N = 205)	4.40 (3.074, 5.717)				

Abbreviations: ANCOVA = analysis of covariance; BMD = bone mineral density; CI = confidence interval; Equiv. = equivalence; IMP = investigational medicinal product; IQC = instrument quality control; N = number of subjects in the analysis set; Non-Inf. = non inferiority; Non-Sup. = non-superiority; PPS = Per Protocol Analysis Set; PSE = principal stratum estimand; SAP = Statistical Analysis Plan; US = United States; Xcal = cross calibration; %CfB = percent change from baseline.

ICE1: Intercurrent Event 1. The first and/or the second dose of randomised IMP is not administered.

ICE2: Intercurrent Event 2 The participant received other medication alongside the IMP, which affects the primary variable (Appendix 16.1.1, Section 6.5.1).

The analysis was performed with an ANCOVA model with %CfB in lumbar spine BMD at Week 52 as the dependent variable; covariates are treatment arm (RGB-14-P and US-licensed Prolia), stratification factors at randomisation (previous use of bisphosphonates [yes/no] and geographical region [Europe, US]), Baseline BMD value in lumbar spine, machine type and machine type*baseline BMD value interaction. Estimated difference: RGB-14-P - Prolia.

BMD analysed in this table is corrected for IQC and Xcal.

Equivalence was claimed if the estimated difference lower limit (left-side) of the two-sided 95% CI was greater than -1.45 and the upper limit (right side) was lower than 1.45; details in the SAP, Version 1.0 (Appendix 16.1.9).

Source: Table 14.2.4.3

Table 47: Analysis of Lumbar Spine BMD at Week 52 - Secondary Principal Stratum Estimand - Sensitivity Tipping Point Analysis (PPS for Main Period)

Characteristic	Value
Proportion of being observe PPSC & PSE patients in the US-licensed Prolia (p0)	84.7
Proportion of being observe PPSC & PSE patients in the RGB-14-P (p1)	88.3
Boundaries for the range of πss:	
Lower limit: max(0, p0-p1)	0
Upper limit: min(p0, 1-p1)	11.7
πss=0%	
Number of tested points (β0, β1)	5041
Number and percentage of 95% confidence interval with LCL > -1.45 and UCL <1.45	5041 (100%)
πss=5%	
Number of tested points (β0, β1)	5041
Number and percentage of 95% confidence interval with LCL > -1.45 and UCL <1.45	5041 (100%)
πss=10%	
Number of tested points (β0, β1)	5041
Number and percentage of 95% confidence interval with LCL > -1.45 and UCL <1.45	5041 (100%)
πss=15%	
Number of tested points (β0, β1)	5041
Number and percentage of 95% confidence interval with LCL > -1.45 and UCL <1.45	5041 (100%)
Number of tested points (β0, β1)	20164
Number and percentage of 95% confidence interval with LCL > -1.45 and UCL <1.45	20164 (100%)

Abbreviations: LCL = lower confidence limit; PPSC = per protocol and completer; PSE = principal stratum estimand; UCL = upper confidence limit; US = United States.

Source: Table 14.2.4.4.1

Secondary efficacy endpoints

Table 48: Percent change from baseline in BMD, secondary endpoints (FAS) (Main Period)

Time Point	Study Treatment	Adjusted Means (95% CI)	Estimated Difference (95% CI)	P-value
%CfB in total hip BMD				
Day 1 - Week 26	RGB-14-P (n=225)	1.14 (0.375, 1.913)	-0.31 (-0.792, 0.165)	0.199
	Prolia (n=211)	1.46 (0.695, 2.220)		
Day 183 - Week 52	RGB-14-P (n=220)	2.16 (1.379, 2.942)	-0.17 (-0.691, 0.347)	0.514
	Prolia (n=205)	2.33 (1.557, 3.108)		
%CfB in lumbar spine BMD				
Day 1 - Week 26	RGB-14-P (n=227)	2.51 (1.339, 3.675)	0.04 (-0.698, 0.775)	0.918
	Prolia (n=218)	2.47 (1.321, 3.617)		
Day 183 - Week 52	RGB-14-P (n=222)	4.63 (3.472, 5.793)	0.37 (-0.340, 1.083)	0.306
	Prolia (n=206)	4.26 (3.119, 5.403)		
%CfB in femoral neck BMD				
Day 1 - Week 26	RGB-14-P (n=225)	0.74 (-0.310, 1.798)	-0.12 (-0.727, 0.478)	0.685
	Prolia (n=211)	0.87 (-0.184, 1.921)		
Day 183 - Week 52	RGB-14-P (n=220)	1.26 (0.187, 2.341)	-0.32 (-1.007, 0.359)	0.351
	Prolia (n=205)	1.59 (0.511, 2.665)		

Table 49: Percent change from baseline in BMD, secondary endpoints (Transition Period)

Time Point	Statistic	RGB-14-P to RGB-14-P (N = 63)	Prolia to RGB-14-P (N = 62)	Prolia to Prolia (N = 63)	Overall Study (N = 188)
%CfB in total hip BMD					
Day 1 - Week 78	n (%)	62 (98.4)	62 (100)	60 (95.2)	184 (97.9)
	Mean	4.24	4.12	4.95	4.43
	SD	3.381	3.128	3.849	3.462
%CfB in lumbar spine BMD					
Day 1 - Week 78	n (%)	63 (100)	62 (100)	60 (95.2)	185 (98.4)
	Mean	7.03	7.06	7.09	7.06
	SD	3.828	4.327	4.240	4.112
%CfB in femoral neck BMD					
Day 1 - Week 78	n (%)	63 (100)	62 (100)	60 (95.2)	185 (98.4)
	Mean	3.08	3.06	4.04	3.39
	SD	4.259	3.337	4.764	4.158

Table 50: Summary of Vertebral Fragility Fractures - Main Period (FAS for Main Period)

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Fractures by Week 52	n (%) E	4 (1.7) 7	8 (3.5) 9	12 (2.5) 16
	95% CIs	0.5, 4.2	1.5, 6.7	1.3, 4.4
	Proportion	0.017	0.035	0.025
	95% CIs for proportion	0.005, 0.042	0.015, 0.067	0.013, 0.044
	% difference	-1.8		
	95% CIs for % difference	-5.2, 1.2		
	Proportion difference	-0.018		
	95% CIs for proportion difference	-0.052, 0.012		

Post-randomisation fractures are summarised in this table.

Abbreviations: CI = confidence interval for proportion of subjects with at least one post-randomisation fracture; E = number of fractures; N = the number of subjects in the analysis set; n = the number of subjects in the specific category.

%: calculated using the number of subjects in the analysis set as the denominator (n/N*100).

Proportion: calculated using the number of subjects in the analysis set as the denominator (n/N).

Difference: RGB-14-P - Prolia.

95% CI calculation is based on Clopper-Pearson method. 95% CI for difference is calculated based on Miettinen-Nurminen (score) method.

Source: Table 14.2.7.1.1

Table 51: Sensitivity Summary of Vertebral fragility fractures - Main Period (FAS for Main Period)

Gedeon Richter Plc. RGB-14-101
Main period (Week 52) analysis Page 1 of 1
Main period dataset Data version: 13-Dec-2023
Table 14.2.7.2.1 Sensitivity Summary of Vertebral fragility fractures - Main period (Full Analysis Set for Main Period)

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Fractures by week 52	n (%) E	18 (7.4) 92	15 (6.5) 45	33 (7.0) 137
	95% CIs	4.5 , 11.5	3.7 , 10.5	4.9 , 9.7
	Proportion	0.074	0.065	0.070
	95% CIs for proportion	0.045 , 0.115	0.037 , 0.105	0.049 , 0.097
	% difference	0.9		
	95% CIs for % difference	-3.8 , 5.7		
	Proportion difference	0.009		
	95% CIs for proportion difference	-0.038 , 0.057		

Post-randomization fractures are summarised in this table; as a sensitivity analysis, vertebras received as non-assessable Genant score were here considered as vertebras with emergent fracture.
CI: Confidence Interval for proportion of subjects with at least one post-randomization fracture.
N: The number of subjects in the analysis set; n: The number of subjects in the specific category; E: Number of fractures;
%: calculated using the number of subjects in the analysis set as the denominator (n/N*100).
Proportion: calculated using the number of subjects in the analysis set as the denominator (n/N).
Difference: RGB-14-P - Prolia.
95% CI calculation is based on Clopper-Pearson. 95% CI for difference is calculated based on Miettinen-Nurminen (score) method.

Reference Listing: 16.2.6.4

/unblinded/gedeo252679/stats/interim_main/prog/tables/t_admo_vff.sas/15APR2024 11:14

Table 52: Summary of Vertebral Fragility Fractures - Transition Period (FAS for Transition Period)

Characteristic	Statistic	RGB-14-P to RGB-14-P (N = 63)	Prolia to RGB-14-P (N = 62)	Prolia to Prolia (N = 63)	Overall Study (N = 188)
Fractures between Week 52 and Week 78	n (%) E	3 (4.8) 10	4 (6.5) 10	2 (3.2) 3	9 (4.8) 23
	95% CIs	1.0, 13.3	1.8, 15.7	0.4, 11.0	2.2, 8.9
	Proportion	0.048	0.065	0.032	0.048

	95% CIs for proportion	0.010, 0.133	0.018, 0.157	0.004, 0.110	0.022, 0.089
	% difference	1.6	3.3		
	95% CIs for % difference	-6.8, 10.4	-5.3, 12.8		
	Proportion difference	0.016	0.033		
	95% CIs for proportion difference	-0.068, 0.104	-0.053, 0.128		
Fractures by Week 78	n (%) E	3 (4.8) 10	4 (6.5) 11	2 (3.2) 4	9 (4.8) 25
	95% CIs	1.0, 13.3	1.8, 15.7	0.4, 11.0	2.2, 8.9
	Proportion	0.048	0.065	0.032	0.048
	95% CIs for proportion	0.010, 0.133	0.018, 0.157	0.004, 0.110	0.022, 0.089

For fractures between Week 52 and Week 78, fractures post-randomization for the Transition Period are summarised. For fractures by Week 78, fractures post-randomization on TP1D1 are summarised.

Abbreviations: CI = Confidence Interval for proportion of subjects with at least one post-randomization fracture. N = The number of subjects in the analysis set; n = The number of subjects in the specific category; E = Number of fractures.

%: calculated using the number of subjects in the analysis set as the denominator (n/N*100).

Proportion: calculated using the number of subjects in the analysis set as the denominator (n/N).

Reference arm: Prolia to Prolia.

95% CI calculation was based on Clopper-Pearson method. 95% CI for difference was calculated based on Miettinen-Nurminen (score) method.

Source: Table 14.2.7.1.3

Table 53: Sensitivity Summary of Vertebral fragility fractures at Week 78 (FAS for Transition Period)

Statistic	RGB-14-P to RGB-14-P (N = 63)	Prolia to RGB-14-P (N = 62)	Prolia to Prolia (N = 63)	Overall Study (N = 188)
Fractures between Week 52 and Week 78				
n (%) E	7 (11.1) 36	6 (9.7) 13	5 (7.9) 15	18 (9.6) 64
95% CIs	4.6 , 21.6	3.6 , 19.9	2.6 , 17.6	5.8 , 14.7
Proportion	0.111	0.097	0.079	0.096
95% CIs for proportion	0.046 , 0.216	0.036 , 0.199	0.026 , 0.176	0.058 , 0.147
% difference	3.2	1.7		
95% CIs for % difference	-7.8 , 14.5	-9.1 , 12.8		
Proportion difference	0.032	0.017		
95% CIs for proportion difference	-0.078 , 0.145	-0.091 , 0.128		
Fractures by Week 78				
n (%) E	8 (12.7) 45	7 (11.3) 17	5 (7.9) 16	20 (10.6) 78
95% CIs	5.6 , 23.5	4.7 , 21.9	2.6 , 17.6	6.6 , 16.0
Proportion	0.127	0.113	0.079	0.106
95% CIs for proportion	0.056 , 0.235	0.047 , 0.219	0.026 , 0.176	0.066 , 0.160

For fractures between Week 52 and Week 78, fractures post-randomization for the Transition Period are summarised. For fractures by Week 78, fractures post-randomization on TP1D1 are summarised.
Abbreviations: CI = Confidence Interval for proportion of subjects with at least one post-randomization fracture; N = The number of subjects in the analysis set; n = The number of subjects in the specific category; E = Number of fractures.
*%: calculated using the number of subjects in the analysis set as the denominator (n/N*100).*
Proportion: calculated using the number of subjects in the analysis set as the denominator (n/N).
Reference arm: Prolia to Prolia.
95% CI calculation was based on Clopper-Pearson method. 95% CI for difference was calculated based on Miettinen Nurminen (score) method.

Table 54: Summary of Non-vertebral fractures - Main Period FAS for Main Period

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Fractures by Week 52	n (%) E	4 (1.7) 6	10 (4.3) 12	14 (3.0) 18
	95% CIs	0.5, 4.2	2.1, 7.8	1.6, 4.9
	Proportion	0.017	0.043	0.030
	95% CIs for proportion	0.005, 0.042	0.021, 0.078	0.016, 0.049

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
	% difference	-2.7		
	95% CIs for % difference	-6.3, 0.4		
	Proportion difference	-0.027		
	95% CIs for proportion difference	-0.063, 0.004		

Post-randomisation fractures are summarised in this table.

Abbreviations: CI = confidence interval for proportion of subjects with at least one post-randomisation fracture; E = number of fractures; N = the number of subjects in the analysis set; n = the number of subjects in the specific category.

%: calculated using the number of subjects in the analysis set as the denominator (n/N*100).

Proportion: calculated using the number of subjects in the analysis set as the denominator (n/N).

Difference: RGB-14-P - Prolia.

95% CI calculation is based on Clopper-Pearson method. 95% CI for difference is calculated based on Miettinen-Nurminen (score) method.

Source: Table 14.2.8.1

Table 55: Summary of Non-vertebral Fragility Fractures - Transition Period (FAS for Transition Period)

Characteristic	Statistic	RGB-14-P to RGB-14-P (N = 63)	Prolia to RGB-14-P (N = 62)	Prolia to Prolia (N = 63)	Overall Study (N = 188)
Fractures between Week 52 and Week 78	n (%) E	1 (1.6) 1	0	1 (1.6) 1	2 (1.1) 2
	95% CIs	0.0, 8.5	NA, NA	0.0, 8.5	0.1, 3.8
	Proportion	0.016	0.000	0.016	0.011
	95% CIs for proportion	0.000, 0.085	NA, NA	0.000, 0.085	0.001, 0.038
	% difference	0.0	-1.6		
	95% CIs for % difference	-7.1, 7.1	-8.5, 4.3		
	Proportion difference	0.000	-0.016		
	95% CIs for proportion difference	-0.071, 0.071	-0.085, 0.043		
Fractures by Week 78	n (%) E	2 (3.2) 2	5 (8.1) 6	3 (4.8) 3	10 (5.3) 11
	95% CIs	0.4, 11.0	2.7, 17.8	1.0, 13.3	2.6, 9.6
	Proportion	0.032	0.081	0.048	0.053
	95% CIs for proportion	0.004, 0.110	0.027, 0.178	0.010, 0.133	0.026, 0.096

For fractures between Week 52 and Week 78, fractures post-randomization for the Transition Period are summarised. For fractures by Week 78, fractures post-randomization on TP1D1 are summarised.

Abbreviations: CI = Confidence Interval for proportion of subjects with at least one post-randomization fracture; N = The number of subjects in the analysis set; n = The number of subjects in the specific category; E = Number of fractures.

%: calculated using the number of subjects in the analysis set as the denominator (n/N*100).

Proportion: calculated using the number of subjects in the analysis set as the denominator (n/N).

Reference arm: Prolia to Prolia.

95% CI calculation was based on Clopper-Pearson method. 95% CI for difference was calculated based on Miettinen-Nurminen (score) method.

Source: Table 14.2.8.3

The primary pharmacodynamic analysis of AUEC of Percent Change from Baseline in sCTX (0-m6) Concentration Until Week 26 and the secondary pharmacodynamic analysis of Percent Change from Baseline in sCTX at Weeks 4, 26, and 52 as well as of Percent Change from Baseline in Serum P1NP at Weeks 4, 26, and 52 are presented in the Clinical pharmacology section above.

Ancillary analyses

Not applicable.

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 56: Summary of efficacy for trial RGB-14-101

Title: A Randomised, Double blind, Multicentre Phase III Study to Assess the Efficacy and Safety of RGB-14-P Compared to Prolia in Women with Postmenopausal Osteoporosis			
Study identifier	Study No.: RGB-14-101 EudraCT No.: 2020-006017-38 IND: 146025		
Design	Randomised, double-blind, multicentre, multiple fixed-dose, 2-arm parallel-group with a transition period		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks (randomised treatment period) 5 weeks (screening period) 26 weeks (transition period)
Hypothesis	Equivalence		
Treatments groups	RG-14-P (test product)		Denosumab 60 mg subcutaneous injection every 26 weeks, administered on Day 1 of Treatment Period 1 and on Day 1 of Treatment Period 2; n = 242
	Prolia (comparator)		Denosumab 60 mg subcutaneous injection every 26 weeks, administered on Day 1 of Treatment Period 1 and on Day 1 of Treatment Period 2; n = 231
Endpoints and definitions	Primary endpoint	PE1	Percent change from baseline in lumbar spine bone mineral density at Week 52 (%CfB in lumbar spine BMD at Week 52)
	Primary endpoint	PE2	Area under the effective curve after the first dose until Week 26 (Day 183) of percent change from baseline serum type I collagen C-telopeptide up to month 6 (AUEC of %CfB $sCTX_{0\text{-}m6}$ until Week 26)
	Secondary endpoint	SE1a	%CfB in total hip BMD at Weeks 26, 52, and 78
	Secondary endpoint	SE1b	%CfB in lumbar spine BMD at Weeks 26 and 78
	Secondary endpoint	SE1c	%CfB in femoral neck BMD at Weeks 26, 52, and 78
	Secondary endpoint	SE1d	Vertebral fragility fracture incidence at Weeks 52 and 78
	Secondary endpoint	SE1e	Non-vertebral fragility fracture incidence at Weeks 52 and 78
	Secondary endpoint	SE2a	%CfB in serum P1NP at Weeks 4, 26, 52, and 78
	Secondary endpoint	SE2b	%CfB in sCTX at Weeks 4, 26, 52, and 78

Database lock	Week 52 DBL: 14 December 2023 Week 78 DBL: 13 February 2024

Results and analysis			
Analysis description	**Primary endpoint (PE1; %CfB in lumbar spine BMD)**		
Analysis population and time point description	Full Analysis Set (FAS) The FAS was defined as all participants to whom the investigational medicinal product had been randomised. Week 52/EOT from baseline		
Descriptive statistics and estimate variability	Treatment group	RGB-14-P	Prolia
	Number of subjects	242	231
	Adjusted Means (95% CI)	4.89 (3.547, 6.235)	4.55 (3.220, 5.874)
	Estimated Difference (95% CI)	0.34 (-0.402, 1.090)	
	Equiv. Claim	Met	
Notes	The analysis was performed with an ANCOVA model with %CfB in lumbar spine BMD at Week 52 as the dependent variable; covariates are treatment arm (RGB-14-P and US-licensed Prolia), stratification factors at randomisation (previous use of bisphosphonates [yes/no] and geographical region [Europe, US]), baseline BMD value in lumbar spine, machine type and machine type*baseline BMD value interaction. Estimated difference: RGB-14-P - Prolia. The estimated difference for the equivalence test between the two treatment groups was 0.34 (95% CI = -0.402, 1.090), which was completely contained within the equivalence margin of -1.45 and 1.45. The equivalence claim was met.		
Analysis description	**Primary endpoint (PE2; AUEC of %CfB $sCTX_{0-m6}$)**		
Analysis population and time point description	Pharmacodynamic Analysis Set (PDS) The PDS was defined as all participants in the safety population with at least one evaluable pharmacodynamic parameter (%CfB and AUEC) and who do not have any protocol deviations that have a relevant impact on sCTX or serum P1NP measurements. Week 26 from baseline		
Descriptive statistics and estimate variability	Treatment group	RGB-14-P	Prolia
	Number of subjects	242	229
	Geometric Mean (95% CI)	13501.30 (12737.814, 14264.794)	13344.65 (12583.291, 14106.002)
	Geometric Mean Ratio (95% CI)	1.01 (0.978, 1.046)	
	P-value	0.494	
Notes	The analysis was performed with a mixed-effects model ANCOVA on natural log transformed AUEC data as the dependent variable and the following model covariates: treatment arm, stratification factors (previous use of bisphosphonates [yes/no] and geographical region [Europe, US]), log of baseline sCTX.		

	In this presentation of results, log-scale fitted mean and treatment group differences (RGB-14-P - Prolia), together with associated 95% CIs were back-transformed. Delta method was applied to back transform geometric mean standard error used for the computation of corresponding 95% CIs. Pharmacodynamic equivalence was concluded as the 95% CI of the treatment geometric mean ratio was contained within the 80% to 125% equivalence margin.

Analysis description	**Secondary endpoint (SE1a; %CfB in total hip BMD)**		
Analysis population and time point description	FAS Weeks 26, 52 and 78 from baseline		
Descriptive statistics and estimate variability	Treatment group	RGB-14-P	Prolia
	Time Point	Day 1 – Week 26	
	Number of subjects	225	211
	Adjusted Means (95% CI)	1.14 (0.375, 1.913)	1.46 (0.695, 2.220)
	Estimated Difference (95% CI)	-0.31 (-0.792, 0.165)	
	P-value	0.199	
	Time Point	Day 183 – Week 52	
	Number of subjects	220	205
	Adjusted Means (95% CI)	2.16 (1.379, 2.942)	2.33 (1.557, 3.108)
	Estimated Difference (95% CI)	-0.17 (-0.691, 0.347)	
	P-value	0.514	
Notes	The analysis is performed with a mixed model repeated measures with observed %CfB in total hip BMD as the dependent variable; covariates are treatment arm (RGB-14-P and US-licensed Prolia), stratification factors at randomisation (previous use of bisphosphonates [yes/no] and geographical region [Europe, US]), Baseline BMD value in total hip, machine type and machine type*baseline BMD value interaction, study week and study week*treatment arm interaction. The treatment differences between RGB-14-P and Prolia groups were not statistically significant at Week 26 and at Week 52.		
Analysis description	**Secondary endpoint (SE1b; %CfB in lumbar spine BMD)**		
Analysis population and time point description	FAS Weeks 26 and 78 from baseline		
Descriptive statistics and estimate variability	Treatment group	RGB-14-P	Prolia
	Time Point	Day 1 - Week 26	
	Number of subjects	227	218
	Adjusted Means (95% CI)	2.51 (1.339, 3.675)	2.47 (1.321, 3.617)
	Estimated Difference (95% CI)	0.04 (-0.698, 0.775)	
	P-value	0.918	
Notes	The analysis is performed with a mixed model repeated measures with observed %CfB in total hip BMD as the dependent variable; covariates are treatment arm (RGB-14-P and US-licensed Prolia), stratification factors at		

	randomisation (previous use of bisphosphonates [yes/no] and geographical region [Europe, US]), Baseline BMD value in total hip, machine type and machine type*baseline BMD value interaction, study week and study week*treatment arm interaction. The treatment differences between RGB-14-P and Prolia groups were not statistically significant at Week 26.

Analysis description	**Secondary endpoint (SE1c; %CfB in femoral neck BMD)**		
Analysis population and time point description	FAS Weeks 26, 52 and 78 from baseline		
Descriptive statistics and estimate variability	Treatment group	RGB-14-P	Prolia
	Time Point	Day 1 - Week 26	
	Number of subjects	225	211
	Adjusted Means (95% CI)	0.74 (-0.310, 1.798)	0.87 (-0.184, 1.921)
	Estimated Difference (95% CI)	-0.12 (-0.727, 0.478)	
	P-value	0.685	
	Time Point	Day 183 - Week 52	
	Number of subjects	220	205
	Adjusted Means (95% CI)	1.26 (0.187, 2.341)	1.59 (0.511, 2.665)
	Estimated Difference (95% CI)	-0.32 (-1.007, 0.359)	
	P-value	0.351	
Notes	The analysis is performed with a mixed model repeated measures with observed %CfB in total hip BMD as the dependent variable; covariates are treatment arm (RGB-14-P and US-licensed Prolia), stratification factors at randomisation (previous use of bisphosphonates [yes/no] and geographical region [Europe, US]), Baseline BMD value in total hip, machine type and machine type*baseline BMD value interaction, study week and study week*treatment arm interaction. The treatment differences between RGB-14-P and Prolia groups were not statistically significant at Week 26 and at Week 52.		
Analysis description	**Secondary endpoint (SE1d; Vertebral fragility fracture incidence)**		
Analysis population and time point description	FAS Weeks 52 and 78		
Descriptive statistics and estimate variability	Treatment group	RGB-14-P	Prolia
	Time Point	Week 52	
	Number of subjects	242	231
	n (%) E	4 (1.7) 7	8 (3.5) 9
	95% CIs	0.5, 4.2	1.5, 6.7
	Proportion (95% CI)	0.017 (0.005, 0.042)	0.035 (0.015, 0.067)
	% difference (95% CI)	-1.8 (-5.2, 1.2)	
	Proportion difference	-0.018	

	(95% CI)	(-0.052, 0.012)	
Notes	Post-randomisation fractures are summarised in this table. Abbreviations: CI = confidence interval for proportion of subjects with at least one post-randomisation fracture; E = number of fractures; N = the number of subjects in the analysis set; n = the number of subjects in the specific category. %: calculated using the number of subjects in the analysis set as the denominator (n/N*100). Proportion: calculated using the number of subjects in the analysis set as the denominator (n/N). Difference: RGB-14-P - Prolia. 95% CI calculation is based on Clopper-Pearson method. 95% CI for difference is calculated based on Miettinen-Nurminen (score) method. The proportion difference between the RGB-14-P and Prolia groups was not statistically significant at Week 52.		
Analysis description	**Secondary endpoint (SE1e; Non-vertebral fragility fracture incidence)**		
Analysis population and time point description	FAS Weeks 52 and 78		
Descriptive statistics and estimate variability	Treatment group	RGB-14-P	Prolia
	Time Point	Week 52	
	Number of subjects	242	231
	n (%) E	4 (1.7) 6	10 (4.3) 12
	95% CIs	0.5, 4.2	2.1, 7.8
	Proportion (95% CI)	0.017 (0.005, 0.042)	0.043 (0.021, 0.078)
	% difference (95% CI)	-2.7 (-6.3, 0.4)	
	Proportion difference (95% CI)	-0.027 (-0.063, 0.004)	
Notes	Post-randomisation fractures are summarised in this table. Abbreviations: CI = confidence interval for proportion of subjects with at least one post-randomisation fracture; E = number of fractures; N = the number of subjects in the analysis set; n = the number of subjects in the specific category. %: calculated using the number of subjects in the analysis set as the denominator (n/N*100). Proportion: calculated using the number of subjects in the analysis set as the denominator (n/N). Difference: RGB-14-P - Prolia. 95% CI calculation is based on Clopper-Pearson method. 95% CI for difference is calculated based on Miettinen-Nurminen (score) method.		

	The proportion difference between the RGB-14-P and Prolia groups was not statistically significant at Week 52.		
Analysis description	**Secondary endpoint (SE2a; %CfB in serum P1NP)**		
Analysis population and time point description	PDS Weeks 4, 26, 52 and 78 from baseline		
Descriptive statistics and estimate variability	Treatment group	RGB-14-P	Prolia
	Number of subjects	241	229
	Time Point	TP1 Day 30 – Week 4	
	n (%)	234 (97.1)	220 (96.1)
	Mean (SD)	22.10 (14.905)	20.22 (15.091)
	Median	23.53	21.52
	Minimum, Maximum	-28.8, 76.6	-36.8, 57.3
	Time Point	TP2 Day 1 – Week 26	
	n (%)	216 (89.6)	211 (92.1)
	Mean (SD)	65.92 (17.828)	62.89 (29-294)
	Median	70.16	68.72
	Minimum, Maximum	-83.0, 89.5	-243.7, 89.9
	Time Point	TP2 Day 183 - Week 52	
	n (%)	204 (84.6)	199 (86.9)
	Mean (SD)	65.04 (19.131)	64.14 (21.591)
	Median	70.29	70.16
	Minimum, Maximum	-53.8, 89.2	-61.7, 91.3
Notes	The median %CfB in the P1NP concentration was comparable between the RGB-14-P and Prolia treatment groups at Weeks 4, 26, and 52.		
Analysis description	**Secondary endpoint (SE2b; %CfB in serum sCTX)**		
Analysis population and time point description	PDS Weeks 4, 26, 52 and 78 from baseline		
Descriptive statistics and estimate variability	Treatment group	RG-14-P	Prolia
	Number of subjects	241	229
	Time Point	TP1 Day 30 – Week 4	
	n (%)	234 (97.1)	220 (96.1)
	Mean (SD)	85.87 (9.567)	85.38 (15.501)
	Median	88.89	88.98
	Minimum, Maximum	40.6, 95.7	-83.9, 96.2

	Time Point	TP2 Day 1 – Week 26	
	n (%)	216 (89.6)	211 (92.1)
	Mean (SD)	69.74 (23.212)	61.51 (83.764)
	Median	75.95	75.47
	Minimum, Maximum	-45.4, 94.3	-1057.1, 93.0
	Time Point	TP2 Day 183 - Week 52	
	n (%)	204 (84.6)	199 (86.9)
	Mean (SD)	62.90 (28.995)	58.84 (63.566)
	Median	70.49	70.90
	Minimum, Maximum	-41.7, 93.3	-651.8, 93.0
Notes	The median %CfB in the sCTX concentration was comparable between the RGB-14-P and Prolia treatment groups at Weeks 4, 26, and 52.		

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme of RGB-14-P to demonstrate biosimilarity to the reference product (Xgeva/Prolia) comprised one phase 1 study (RGB-14-001) and one phase 3 study (RGB-14-101). The phase 1 study was a randomised, double-blind, single 60 mg fixed dose, parallel study to compare PK/PD, safety and immunogenicity of RGB-14-X vs. US-Xgeva in healthy male volunteers. The phase 3 study is a randomised, double-blind, parallel, multicenter, multinational study to compare the efficacy and safety of RGB-14-P vs. US-Prolia in postmenopausal women with osteoporosis.

There are no ongoing or planned studies. The clinical development plan is acceptable and sufficient to support the biosimilarity to Xgeva/Prolia. The use of US sourced reference material has been discussed in the EMA Scientific Advice procedure (EMA/CHMP/SAWP/338801/2019 and EMA/CHMP/SAWP/260988/2020) and can be agreed with, given that demonstration of analytical comparability between the US- and the European Union-sourced reference materials served as an adequate bridge (as mandated in CHMP/437/04 Rev 1).

The Main Period of Study RGB-14-101 has been completed, while the Transition Period was still ongoing at DCO at the time of initial submission. The RGB-14-101 Clinical Study Report (CSR) is only covering the Main Period of 52 weeks. The duration of the Main Treatment Period of 12 months is considered appropriate for the evaluation of efficacy based on the percent change from baseline in lumbar spine BMD at Week 52 (primary efficacy endpoint). The Week 78 clinical data are considered supportive to enable evaluation of long-term clinical equivalence. The final study report containing the final data up to Week 78 for all patients have been provided during the procedure.

RGB-14-101 study design

The study consists of two periods; the two-arm Main Treatment period (52 weeks) which consisted of Treatment Period (TP) 1 (26 weeks) and TP 2 (26 weeks). Patients received 2 injections of either RGB-14-P or US-Prolia at 6-month intervals (On Day 1 of TP1 and Day 1 of TP2); and a three-arm Transition Period (26 weeks) during which patients received an additional dose. Patients who received Prolia during the Main Period were to be re-randomised (1:1) to receive either a dose of RGB-14-P or Prolia in a double-blinded manner. Patients who received RGB-14-P during the Main Period would continue to receive a dose of RGB-14-P but would also follow the randomisation procedure to maintain blinding. The duration of the Main Treatment Period of 12 months for the evaluation of efficacy based on the co-primary efficacy endpoints percent change from baseline in lumbar spine BMD at Week 52 and AUEC of s-CTX over the initial 6 months between RGB-14-P and US-licensed Prolia is considered appropriate and in accordance with CHMP scientific advice (EMEA/H/SA/4137/1/2019/III).

The duration of the Transition period is another 6 months, as requested by the FDA, and allows assessment of switching from Prolia to RGB-14-P, but also provides additional PK, PD, efficacy and safety data for those patients who continue on the same treatment as initially assigned. The overall study design is deemed acceptable and in agreement with other recently approved biosimilar medicines for Prolia and Xgeva.

Study population:

Female patients with postmenopausal osteoporosis (PMO) are considered the most sensitive population with respect to the approved indications to assess the biosimilarity between RGP-14-P and the reference product in terms of efficacy, safety, and immunogenicity, and is consistent with the Scientific Advice from EMA (2019).

Inclusion & Exclusion Criteria

Inclusion of postmenopausal women with a T-score ≤ -2.5 and ≥ -4.0 at the lumbar spine as measured by dual energy X-ray absorptiometry (DXA), aligns with the state-of-the-art definition of osteoporosis, and using DXA is the gold standard for assessing bone mineral density (BMD). The exclusion of patients with T-score below -4.0 is also endorsed to reduce inter-subject variability of PMO patients. Evaluation of an additional hip joint besides lumbar spine evaluation was not listed in the inclusion criteria, but according to Efficacy measurements it has been performed.

It is known that BMD relates to age and the 10-year probability of major osteoporotic fractures starts to increase more rapidly after the age of about 65 years. In that regard, the set age range (≥ 60 and ≤ 90 years at the time of signing the informed consent) may introduce heterogeneity to the study population, e.g. due to age-related comorbidities. The maximum age was 83 in RGB-14-P group and 84 in the Prolia group age, with an overall mean age (standard deviation [SD]) of 66.7 (5.06) years. Age was evenly distributed between groups and only 3 patients in the RGB-14-P group and 2 patients in the Prolia group were aged over 80 years. Thus, this is not further pursued.

The study specified body weight limits (≥50 kg and ≤99.9 kg) in the inclusion criteria, which is endorsed. Lower and upper body weight limits aim to enhance population homogeneity, as body weights may be related to the baseline BMD and potentially affect the treatment's impact on BMD.

Current heavy smokers were excluded from the analysis. Therefore, current light and heavy ex-smokers have been allowed to be recruited. While it is appreciated that smoking is a risk factor for osteoporosis, the FRAX tool, widely used in clinical practice to predict the 10-year fracture risk of the patient, only considers the 'currently smoking' status.

Prior to study medication, specifically bisphosphonates, fluoride, or strontium, can impact bone metabolism, influencing study outcomes. Inclusion of patients with prior bisphosphonate use, whether parenteral or oral, is expected to cause heterogeneity in the study population due to the inhibitory effect of bisphosphonates on bone turnover that can last for several years after cessation of medication. The washout periods for previous osteoporosis treatments are adequately reflected. Prior bisphosphonates therapy (Yes vs. No) was used as stratification factor in the randomisation and covariate in the statistical analyses. This is acceptable.

Randomisation and blinding:

Blinding during both Main Period and Transition Period is maintained. This is acceptable.

As the IMP pre-filled syringes were not blinded, the pharmacy staff and monitor responsible for checking IMP accountability were unblinded. Unblinded site staff did not perform any clinical assessment. Subjects were blinded by using a mask and noise cancelling headphones during the dosing procedure so that the injection syringe was not visible to them. This procedure is considered acceptable.

As per EMA SA, stratification by age, weight and previous BP use was recommended. Randomisation on Day 1 for the TP1 was stratified by prior use of bisphosphonates (yes/no) and by geographical region (EU/US). Stratification by age (e.g. < 65 years, ≥ 65 years) would have been reasonable given the inclusion of a wide age range. While the recommendation of previous BP use was followed, stratification by region was used as a second stratification factor. This is also considered adequate and ensures a balanced allocation of subjects, although only 20 patients in total were from the US. Stratification by re-randomisation was not performed, which is not necessarily a standard requirement and thus is acceptable.

Overall, both the process of randomization and the process of blinding were adequately described and is considered acceptable.

Trial intervention

During the Main Treatment Period, patients received 60 mg of either RGB-14-P or US-Prolia on Day 1 and at Month 6 as s.c. injections in the upper arm, upper thigh, or abdomen. A third dose of either 60 mg RGB-14-P or US-Prolia was administered at the beginning of the Transition Period at Month 12. This is in line with the posology recommendations from the Prolia SmPC for the treatment of osteoporosis and is regarded adequate for the assessment of biosimilarity of the test and reference product.

Concomitant Therapies

Prohibited concomitant medication and accepted washout periods have been described in the study protocol and were part of the exclusion criteria of study RGB-14-P. If a patient used prohibited concomitant medication during the study, the patients had to discontinue from study drug. Listed prohibited concomitant medications are considered appropriate and, therefore, acceptable.

All subjects received daily supplementation of at least 1000 mg elemental calcium. The dosage of vitamin D was adjusted based on baseline levels. According to Prolia SmPC, patients had to be adequately supplemented with calcium and vitamin D. This is endorsed.

Study assessment

DMX and lateral spine X-rays were used for confirming participant eligibility and assessment changes at Week 26 and Week 52 (EOS/ET) of the Main Period in lumbar spine, total hip and femoral neck BMD or occurrences of vertebral and non-vertebral fractures relative to baseline. Efficacy analyses were based on centrally read results. This is appropriate.

X-ray images were independently read in a blinded fashion by one central reader radiologist. In order to maintain objectivity in the evaluation of imaging, the independent reviewer was blinded to subject name, subject initials, subject date of birth, investigator site identifiers, and imaging dates. The reviewers assessed the study images for technical adequacy and quality. This is acceptable.

Objectives, endpoints and estimands

Primary objective and endpoint

The applicant had different primary and secondary objectives for EMA versus FDA, which is acceptable. Study RGB-14-101 had two primary objectives that aimed at demonstrating equivalent efficacy and PD of RGB-14-101 to US-Prolia in postmenopausal women with osteoporosis. For the EMA, using lumbar spine BMD at Week 52 and sCTX until Week 26 as primary efficacy endpoints is considered acceptable and has been recommended during the EMA SA EMA/CHMP/SAWP/338801/2019. The selection of these endpoints as co-primary endpoints is endorsed and sufficient to demonstrate the similarity in clinical efficacy as it encompasses a clinically relevant outcome and a more dynamic and sensitive surrogate turnover marker. This is also in line with the guideline on osteoporosis (CHMP/EWP/552/95 Rev.2 Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis), which recommends the use of co-primary variables including BMD measured at the spine and/or the hip and appropriate biochemical markers of bone turnover.

The equivalence margin of 1.45% is sufficient to demonstrate equivalence in clinical efficacy and is endorsed and used in other applications for Denosumab biosimilars. It is noted that an equivalence margin of 1.5 is mentioned and endorsed in the Scientific Advice 2019, and is actually wider than the present equivalence margin.

Two intercurrent events (ICEs) were defined for the two co-primary endpoints (ICE1, the first and/or the second dose of the randomised IMP was not administered; ICE2, the participant received other medication alongside the IMP, which affects the primary variable). In a primary estimand a treatment policy strategy (ICE1) and a composite strategy (ICE2), in a secondary estimand a principle stratum estimand was applied. The combination of these two estimand strategies is adequate formulated to assess biosimilarity. Some unclear details were requested.

For the originally submitted primary analysis, the applicant excluded all patients from the analysis with missing values in the outcome variable (originally missing or set to missing after the occurrence of ICE1) without experiencing ICE2. The applicant clarified as per request on ICE definition and strategy that data for the primary endpoint was not collected in case of ICE1 due to "second investigational medicinal product (IMP) dose was not administered". A table with all missing values, corresponding reasons, as asked for, was not provided by the applicant. According to the applicant as per request definition of a new ICE category for "errors or deviation in dosing" was not possible due to "lack of such events".

a. However, to show that the results are robust regarding different handling of missing values and ICEs, the applicant provided a tipping point analysis as sensitivity analysis, in which for every patient in the Prolia group as well as in the RGB-14-P group, missing values (originally missing or set to missing due to ICE1 or ICE2) get imputed by PROC MI with FCS Statement. For patients in the RGB-14-P group (only), additionally a shift ranging from -8.45 to 2.55 was added to the imputed value. The equivalence criterion for this sensitivity analysis was still met when delta (RGB-14-P shift) was between -7.75 and 2.45. Unfortunately, the applicant provided here only 90% confidence intervals. The applicant regarded the two identified tipping points do not represent realistic scenarios. Even if the tipping point is reached much earlier when shifting upwards

compared to shifting downwards, the overall results are considered sufficiently robust and hence the issue is not further pursued.

The secondary estimand is not defined optimally, but it will not change the conclusions resulting from the primary estimand.

Secondary objective and endpoint

The secondary efficacy endpoints Percent Change from Baseline in Lumbar Spine BMD at Weeks 26 and 52, Percent Change from Baseline in Total Hip BMD at Weeks 26 and 52, Percent Change from Baseline in Femoral Neck BMD at Weeks 26 and 52, Vertebral Fragility Fracture Incidence at Week 52, and Non-vertebral Fragility Fracture Incidence at Week 52 were chosen. After the transition (TP3), the same endpoints were assessed at week 78 for a subset of patients. These, besides the secondary pharmacodynamic endpoints are considered clinically relevant and support the primary efficacy endpoints, although they may be less sensitive in detecting differences between treatment groups. Fracture rate is considered more clinically relevant than BMD, as BMD is primarily a surrogate marker for fracture risk and fractures directly impact patient health and quality of life. Despite its clinical relevance, using fracture rate as an endpoint is challenged by its limited occurrence during study period, difficulties in accurately detect and measure fractures and that not all fractures may be disease-related, thereby potentially confounding results. The applicant differentiates between vertebral and non-vertebral fractures, which is preferred over using an undifferentiated fracture rate. Further differentiation of non-vertebral fractures to specifically analyse hip fractures would also be valuable, particularly given the clinical significance of hip fractures in this population. However, it is acknowledged that the number of hip fractures is limited to be analysed separately with adequate statistical power.

The secondary PD endpoints are considered acceptable to support the demonstration of PD similarity of RGB-14-P and US-Prolia. The PD sampling time points are also regarded acceptable.

While the absence of pre-defined equivalence margins for secondary endpoints precludes a definitive conclusion about clinical equivalence, it does not prevent the identification of statistically significant differences between groups. In light of this, it's crucial to discuss the clinical relevance of any observed differences in these secondary endpoints.

Statistical methods for estimation and sensitivity analysis

A model of ANCOVA was implemented to estimate the difference in means between the test and reference arms for percentage CfB of BMD in the lumbar spine at Week 52. This strategy was adequately defined to assess the objective of the trial.

Three sensitivity analyses (imputation of missing primary efficacy post baseline data, secondary estimand tipping point analysis and hypothetical ICE handling strategy) were performed. These might be meaningful in order to assess the impact of missing values.

The sample size calculation can be followed.

Efficacy data and additional analyses

Results

The original version (1.0) of the study protocol (dated 10 March 2021) for study RGB-14-P was amended five times after study initiation (Date of first enrolment: 21 Sept 2021).

The major changes between protocols did not raise any concerns and were mainly done to incorporate responses and suggestions made by the US FDA, changes for statistical analysis, consistency with supporting study documents and suggestions made based on Investigator experiences. The study population was further restricted concerning history and/or present medical conditions, and prior/concomitant medication, while the study was already on-going.

The applicant provided a detailed overview of the protocol amendments and provided all relevant protocol versions. All protocol amendments were initiated prior to database lock and do not seem to be driven by data. The protocol amendments are considered appropriate.

Participant flow and numbers analysed

It is noted that the number of participants that completed the Main Period did not match with number of completed in end of study as a proportion of patients continuing in the Transition Period and did not complete end of study. Numbers and reasons for discontinuation were displayed for the complete Main Period and were comparable between the groups, which is acknowledged. As per request, a flow chart and tables detailing patient disposition by treatment group and treatment period were provided as requested. The participants' flow and progress within the entire study (Main Period + Transition period) is comprehensible and showed that numbers of participants randomised and treated are comparable between treatment groups. The exact numbers of patients entering the Transition Period have been provided.

Protocol deviations

The applicant provided a summary of the number and percentage of subjects with a major protocol deviation from the FAS per Treatment and overall of the Main Period, but again, not by Treatment Period. By-subject listings of all protocol deviations and a Protocol Deviation Specification Document (PDAP) were provided, which detailed the Protocol Deviations of each subject and categorises each event based on its description regarding the impact on data/processes that could potentially affect efficacy and/or safety and lead to exclusion of a subjects from the PPS. Deviations were reviewed and classified in a blinded fashion at the Blinded Data Review Meeting (BDRM) prior to unblinding at the end of Main Treatment Period. The Week 52 and the Week 78 Blinded Data Review Meeting, which specified all major and minor protocol deviations each took place before their database lock and unblinding.

The number of participants with any major protocol deviation were 137 (29%) participants overall in the FAS (65 [26.9%] participants in RGB-14-P group and 72 [32.2%] participants in the Prolia group), with the most common category being procedures/tests (23.7% overall, RGB-14-P: 21.9%, Prolia: 25.5%). Protocol deviations related to COVID-19 were not described, which is remarkable, although the COVID-19 pandemic required specific attention on protocol deviations that may impact study assessments, treatments and follow-up of the subjects.

Protocol deviations due to AE SAE were overall low (n=1 [0.2%]). A total of 4 participants (RGB-14-P: 2 participants and Prolia: 2 participants) was excluded from the PPS due to a major deviation, which was related to the category of meeting an exclusion criterion in 3 participants and to 'other' criteria (involved into another study) in 1 participant. A total of 3 participants (RGB-14-P: 1 participant and Prolia: 2 participants) was excluded from the pharmacodynamic analysis set (PDS). The exclusions to the PDS analysis set were all related to procedures and tests. No participants were excluded from the immunogenicity analysis set (IAS).

The markedly low number of protocol deviations leading to exclusion from the PPS and PDS, and no exclusions from the IAS is noticeable. As per request, the applicant clarified that an impact assessment of protocol deviations was implemented. In the PDAP the protocol deviation categories were pre-assigned to the

major or minor classifications. A number of protocol deviations categories were determined to require a threshold assessment to decide whether it is an important deviation that triggers exclusion from an analysis. The protocol deviations and their potential impact (i.e. their classification) have been reviewed during cyclic reviews of the protocol deviation listings and at the Blind Data Review Meetings. The actions, determination and decisions taken for classification of Protocol deviations as major/minor as well as exclusions from analysis sets are considered appropriate to aim at preserving data integrity and minimising bias.

In particular, the high number of protocol deviations were mainly driven by the category procedures/tests. The applicant was asked to elaborate on the reasons for the high numbers of protocol deviations due to "procedures/tests" and to clarify why exclusions from the PPS (e.g. PD_PT46), PDS (e.g. PD_PT30) and IAS (e.g. PD_PT26) designated in the PDAP were not presented in the CSR Analysis Set. The applicant was able to clarify and justify the high number of PDs in the category "Procedures/Tests". 239 PDs in that category were due to missing erythrocyte sedimentation rate (ESR) value that was originally included in the protocol version 1, but could not be performed centrally. Thus, ESR measurements were omitted, and resulted in 239 PDs until removal from CSP. The majority of PDs in Procedures/Tests stemed from inadherence to the handling requirements of pharmacodynamics samples at sites (853 in total), including sample preparation, where the allowed window for clotting time of PD samples was initially not provided to the sites. This is considered not optimal but the applicant performed validation test to exclude relevant effect on the results. Other deviations concerned the samples collection time violations. No further information were provided but these deviations were apparently handled by a stringent decision tree, which is considered appropriate. Also, PDs related to immunogencity and drug concentration samples were noted but these are not considered to compromise sample integrity, as confirmed by the applicant. Further PDs were missing DXA scans at Week 52, which were excluded from analyses if taken more than 30 days out of schedule. This is in line with other denosumab procedures and deemed acceptable.

Baseline data

Demographic data

The applicant provided summaries in total and by treatment group as well as listing by participant for most baseline characteristics.

The demographic characteristics were well balanced between the RGB-14-P and the US-Prolia group for the FAS. The median age was 66.0 (range 60-83) years and 66.0 (range 80-84) years, respectively. Most of the participants were "White" (99.4%). There were slight imbalances in the demographic distribution regarding ethnic origin and race, but these were negligibly low. In addition, the height, weight and the BMI of the participants were comparable among groups. The presentation of an age category, e.g. by 60 - 70, 70-80, >85 would be appreciated, as well as an BMI category, e.g, by <25, 25 – 30, >30.

Current heavy smokers were excluded from the study Therefore, current light or heavy ex-smokers were allowed to be recruited, but numbers of smokers including smoking status (never, former, current) and classification of smokers (Non-smoker, light smokers and other) have neither been provided in subject summary tables or individual listings. The negative impact of smoking on BMD is well-documented in scientific literature, showing a dose- and age-dependent effect (Kanis 2019, DOI: 10.1007/s00198-018-4704). The inclusion of current smokers in clinical studies can introduce population heterogeneity due to the dose-related and cumulative effects of smoking on bone health (Ward KD and Klesges RC Calcif Tissue Int. 2001, Trevisan C et al. J Clin Densitom. 2020). The applicant clarified as per request that any data on the smoking history/status of the subjects have not been collected, and consequently no classification/sub-group

analysis by smoking habits could be presented. However, the applicant elaborated on some indirect evidence for the homogeneity of the study population in this respect with regard to Serum parathyroid hormone (PTH), serum C-terminal telopeptide (sCTX) and Procollagen 1 N-terminal Propeptide (P1NP) levels as well as vitamin D levels. All these parameters were assessed at baseline, which were found to be well balanced between treatment groups. Based on that, it can be concluded that smokers and non-smokers were evenly distributed across the two study arms.

As per request, further baseline data for fracture history (, history of hypersensitivity, prior use of bisphosphonates including duration of use and Serum 25 (OH) vitamin D level. Alcohol consumption was not recorded. The presented baseline data is equally distributed between treatment groups, which confirms homogeneity of the study population.

Baseline disease characteristics

The baseline characteristics were not presented as overview, but together with the Week 26 and Week 52 measurements for the FAS and the PPS. Also, no T-score values for the lumbar spine (LS), total hip (TH), femoral neck (FN) were presented, but the applicant claimed that the participants had baseline absolute BMD consistent with T-score at the lumbar spine between ≤ -2.5 and ≥ -4.0 as measured by DXA during the Screening Period. Further, no fracture history (including time since latest fracture, anatomical site of fracture, fracture severity) was presented as baseline characteristics. As per request, the applicant provided baseline characteristic overview tables separated by treatment group and overall showing number/percentage, mean, median and min/max values for each LS-BMD by DXA, LS-BMD T-score by DXA, TH-BMD by DXA, FN-BMD by DXA, CTX, PINP, ADA titer and Nab as well as vertebral and non-vertebral fractures. The applicant provided baseline data as requested. Number/percentage, mean, median and min/max values for each Lumbar Spine, Femoral Neck and Total Hip Baseline Bone Mineral Density (g/cm2), baseline serum P1NP and sCTX levels, ADA titer and Nab were all well-balanced between treatment groups. Also, baseline T-scores were balanced between treatment groups although three participants had IQC and XCAL corrected T-score values of -4.1. The applicant explained that their uncorrected T-score values were -4.0, thus they have been considered to be eligible to participate in the study. Although the corrected T-score value is considered the standard to be used for determining eligibility, the number of deviation is negligible low. Thus, it is deemed acceptable to have included them in the study.

As regards vertebral and non-vertebral fractures at baseline, apart from traumatic fractures that were more frequent in the Prolia group, the distribution between groups was considered equal.

Overall, the presented baseline disease characteristics were adequate and balanced between the RGB-14-P and Prolia groups for the Main Period. Also, they were similar between both analysis sets, FAS and PPS. Only one participant in the Prolia group (0.4%) was ADA positive at baseline, which can be neglected.

Medical history and concurrent illnesses

As per request, the applicant provided overview tables of the most frequently reported medical history and concomitant illnesses by SOC (in ≥ 20% participants overall) by treatment group and overall. Despite small imbalances these characteristics are considered unlikely to affect assessments and/or result in great heterogeneity also acknowledging the aged study population with several co-morbidities.

The most frequently reported medical history and concomitant illness by SOC by participants overall included musculoskeletal and connective tissue disorders (82.2% and 81.4%, respectively). The numbers of "Subjects with new osteoporosis diagnosis" (25.8% in total) and "Subjects with prior osteoporosis diagnosis" (74.2% in total) add up to 100%. According to the Summary, 82.8% of participants in total had "musculoskeletal and

connective tissue disorders" listed. Of these, 58.1% overall had "Osteoporosis" and 16.1% overall had "Osteoporosis postmenopausal", totalling 74.2%. This 74.2% corresponds to "Subjects with new osteoporosis diagnosis". Thus, no concerns arise regarding the PMO status. For convenience and coherence, however, it would be appreciated, if the applicant would have also presented the menopause status. Apart from this further "musculoskeletal and connective tissue disorders" history reported were comparable between the RGB-14-P and Prolia treatment groups. Two patients (0.9%) in the Prolia group had Hypercalcaemia listed in the medical history and one patient in the Prolia group had concurrent hypercalcaemia (0.4%).

The other prior and concurrent medical history data for both groups were also comparable among groups by the data available from different SOC groups.

Prior and concomitant treatments

As per request, the applicant provided overview tables of the most frequently reported prior and concomitant medications (in ≥ 10% participants overall) by treatment group and overall. The distribution reflects the co-morbid status of the study participants. Except for HMG CoA reductase inhibitors (35.5% in the RGB-14-P group, 41.6% in the Prolia group), the concomitant medications reported were comparable between the RGB-14-P and Prolia treatment groups. The imbalanced use of HMG CoA reductase inhibitors might be due to the uneven distribution in the System Organ Class Metabolism and nutrition disorders (e.g. Hypercholesterolaemia and HMG CoA reductase inhibitors).

The most frequently reported prior medications included COVID-19 vaccines Vitamin D and analogues calcium preparations, calcium combinations with Vitamin D. Except for of Vitamin D and analogues (21.9% in the RGB-14-P group, 34.2% in the Prolia group) and calcium preparations (12.4% in the RGB-14-P group, 21.6% in the Prolia group), the prior medications seem to be comparable between the RGB-14-P and Prolia treatment groups. Concomitant Vitamin D and analogues, calcium preparations and calcium combinations with Vitamin D were overall reported in 82.9%, 56.2% and 51.4% participants, respectively.

According to the Summary of concomitant medications bisphosphonates (BP) had been used by 16 (6.6%) participants in the RGB-14-P group and 18 (7.8%) participants in the Prolia group (7.2% overall) prior to study begin. No concomitant used is listed by participant. The applicant stratified by prior BP use.

As a conclusion, the population enrolled and analysed can be considered as homogenous as possible, regarding all known variables that may affect BMD and PD results, and reflects the intended indication.

Outcomes and estimation

Primary efficacy endpoint

Based on the FAS, the LS mean estimated difference at Week 52 for the equivalence test using ANCOVA model between the two treatment groups was 0.34 (95% CI = -0.402, 1.090). Thus, the 95% CIs fell within the prespecified efficacy equivalence acceptance range of (-1.45, 1.45), supporting the claim of biosimilarity.

The visit-wise summaries of lumbar spine BMD for the Main Period reveal that compared to the baseline, an increase was observed in the lumbar spine BMD up to Week 52, with a mean %CfB (SD) for the FAS of 5.68 (3.535) in the RGB-14-P and 5.19 (4.118) in the Prolia group. The mean %CfB (SD) for the PPS did not differ much from the FAS (5.68 (3.535) in the RGB-14-P and 5.19 (4.118) in the Prolia group). This is acknowledged.

Sensitivity analysis

As a conclusion, the sensitivity analysis for the primary treatment policy estimand gave very similar results as the primary analysis. The sensitivity results were consistent with the primary analysis conclusion.

Supplementary efficacy analysis

At Week 52, the estimated difference between the two treatment groups was 0.36 (95% CI = -0.373, 1.093) and the p-value was 0.335. Supportive analyses within patients in the PPS who completed the study and did not experience any intercurrent events (i.e., Secondary Principal Stratum Estimand, RGB-14-P, n: 216; Prolia, n: 205) supported the main findings of equivalence for %CfB in lumbar spine BMD at Week 52 between RGB-14-P and Prolia.

Non-inferiority and non-superiority assessment (Analysis according to FDA Scientific Advice)

The non-inferiority claim was met as the lower limit of the two-sides 90% CI was greater than -1.45. The non-superiority claim was met as the upper limit of the two-sided 90% CI was lower than 1.45.

Tipping point analysis (Analysis according to FDA Scientific Advice)

Based on the FAS, the %CfB in lumbar spine BMD at Week 52 for the Main Period under the assumption of all missing data (regular or after ICE2) MAR, a tipping point analysis following two approaches was executed.

The results of the sensitivity analysis of the primary endpoint support the robustness of the equivalence between RGB-14-P and Prolia in terms of the primary efficacy endpoint.

Secondary estimand

The equivalence claim between the two treatment groups in relation to the %CfB in lumbar spine BMD at Week 52 was met. Both superiority and inferiority were rejected. Thus, non-superiority and non-inferiority are claimed.

A sensitivity tipping point analysis of lumbar spine BMD at Week 52 (secondary principal stratum estimand [PSE]) for the PPS for the Main Period found all (5041 [100%]) 95% CIs to be within the lower confidence limit (-1.45) to upper confidence limit (+1.45) range. As a conclusion, the tipping point was not obtained with this range of tested parameters.

Secondary efficacy endpoints (Main Period)

%CfB BMD of vertebral (Lumbar spine) and non-vertebral (Total Hip and Femoral Neck) structures

The data of the secondary efficacy analysis of %CfB BMD of vertebral (Lumbar spine) and non-vertebral (Total Hip and Femoral Neck) structures did not reveal clinically remarkable difference between RGB-14-P and RP and showed similar improvement in BMD of all vertebral and non-vertebral structures over time (Week 26 to Week 52) being supportive for the primary endpoint outcome. The treatment differences between RGB-14-P and Prolia were for these six secondary efficacy variables thus not statistically significant. However, no predefined margins for acceptable were set for secondary endpoints. The analysis of lumbar spine BMD at week 52 was here performed with inclusion of post-ICE2 assessments opposed to the sensitivity analysis of the primary efficacy variable, and the results supported the main findings of equivalence for %CfB in lumbar spine BMD at Week 52 between RGB-14-P and Prolia. The results obtained from FAS and PPS are similar and are supporting the primary endpoint analysis.

All secondary efficacy endpoints at Week 26 were evaluated in the FAS. However, in this analysis set, 14 (3%) participants (RGB-14-P: 6, Prolia: 8) had an intercurrent event 1 (ICE1) where the first dose was not administered in TP 1, and since all randomised subjects received one dose of study intervention, this must

have occurred in TP2. Due to the low and equally distributed number of subjects with ICE1 in the two groups, the issue is not pursued.

Vertebral and non-vertebral fractures

Descriptive statistics of fracture incidence (vertebral and non-vertebral) were provided along with estimation of the proportion difference.

The secondary efficacy variables of vertebral and non-vertebral fragility fracture incidence at week 52 found low number of fractures in both treatment groups. The proportion difference of vertebral fragility fracture incidence between the RGB-14-P and Prolia groups was not statistically significant. Although numerically there were twice as many fractures in the Prolia group [n=8 (3.5%)] compared to the RGB-14-P group [n=4 (1.7%)], the numbers are low and the imbalance is in favour of RGB-14-P. The results obtained from the FAS and the PPS were very similar. Also, the proportion difference of non-vertebral fragility fracture incidence at Week 52 between the RGB-14-P and Prolia groups was not statistically significant. Again, non-vertebral fractures were observed twice as many in the Prolia group [10 (4.3%)] compared to the RGB-14-P group [n=4 (1.7%)].

As a sensitivity analysis, vertebras received as non-assessable Genant score were here considered as vertebras with emergent fracture. There is no statistically significant difference between treatment groups in this sensitivity analysis. The analysis revealed similar results in the FAS compared to the PPS. Vertebral fractures were observed in 4 patients treated with RGB-14-P and in 8 patients treated with the RP. The numbers used for the sensitivity analysis of vertebral fractures (n=18 in the RGB-14-P group and n=15 in the Prolia group) is based on an approach that considers vertebras received as non-assessable Genant score as vertebras with emergent fracture in order to mitigate the risk associated with non-evaluable X-ray on certain vertebras. This is considered acceptable.

As per request, the applicant provided data on baseline vertebral and non-vertebral fracture incidence. The baseline data was balanced between treatment groups.

As per request, the applicant performed primary sensitivity analyses adjusted for, or stratified by age (e.g. < 65 years, ≥ 65 years), which were requested based on inclusion of participants of a wide age range and no stratification for age. The results show that the estimated difference for the equivalence test between the two treatment groups was completely contained within the equivalence margin of -1.45 and 1.45. The applicant was also requested to perform subgroup analysis by smoking habits. The applicant explained that smoking history/status of the subjects have not been collected. However, the applicant provided indirect evidence some PD parameters that have been found in studies to be significantly lower in current smokers compared to non-smokers to be evenly distributed across the two treatment groups. The justification is acceptable.

Concerning age and BMI, the applicant assumed that age and BMI would be evenly distributed between the treatment arms, which is a premise not agreed on. However, as noted by the applicant, the mean age, BMI and weight was levelled between the treatment arms, hereby reducing the need for these covariates to be included in the models. Furthermore, as evident in Q64, the primary analysis with age as a covariate as well as subgroup analyses by age < 65 years and ≥ 65 years showed point estimates and 95% CIs within the allowed equivalence margin of -1.45 to 1.45, thus meeting the claim of non-inferiority. Age does thus not appear to impact the effect of RGB-14-101.

The applicant did not collect information on smoking status in the RGB-14-101, which could have been of value considering the impact of smoking status on bone density and osteoporosis. It is however appreciated that smoking status is a very difficult value to assess properly, that differences between tobacco products

exists and that self-reported smoking use can be unreliable. The applicant argues that laboratory values of PTH, CTX, P1NP and vitamin D can serve as proxy values for smoking status, since the level of these parameters have been found to be altered in smokers vs non-smokers. While the described associations between smoking and these four biochemical factors may also be affected by other factors, the literature does lend support to associations between smoking and these factors, and it is agreed that the levelled baseline values of PTH, CTX, P1NP and vitamin D in the RGB-14-P and Prolia group is reassuring. Furthermore, a previous study (McCloskey et al) reported a similar effect of denosumab on osteoporotic fracture risk in postmenopausal women regardless of being current smoker or not. It is thus acknowledged that albeit smoking being a major risk factor for osteoporosis and not assessed as neither baseline characteristic, nor included in analyses, the lack of data on smoking is not considered to influence the results of the RGB-14-101 study. Generally, the results for the secondary BMD endpoints and fragility fracture incidence rate support the claim of biosimilarity.

As already discussed above, due to the paucity of ADA positive signals, it is difficult to draw meaningful conclusions on the relationship of ADA positive/negative status to efficacy.

Secondary efficacy endpoints (Transition Period)

The %CfB in lumbar spine BMD, total hip BMD and femoral neck BMD up to Week 78 were assessed after re-randomisation of patients in the Prolia group to RGB-14-P or Prolia at Week 52. They were each similar across the treatment groups for the FAS and PPS. Results from the Transition Period (Week 52 to Week 78) are in line with results up to Week 52 concluding that the switching from Prolia to RGB-14-P did not impact the %CfB in total hip BMD, lumbar spine BMD, and femoral neck BMD and improvement was maintained, respectively.

The results of the Sensitivity Analysis Week 78 (Analysis Based on USFDA Scientific Advice) additionally support that switching from Prolia to RGB-14-P did not impact the %CfB in lumbar spine BMD.

The proportion differences of vertebral fragility fracture incidence at Week 78 and non-vertebral fragility fracture incidence at Week 78 between the allocated groups were not statistically significant between Week 52 and Week 78. Additionally, there is no statistically significant difference between treatment groups in the sensitivity analysis that considered vertebras received as non-assessable Genant score as vertebras with emergent fracture.

There were no new non-vertebral fragility fractures on the Prolia to RGB-14-P arm in the Transition Period.

Very similar results were obtained for the PPS. As a conclusion, switching from Prolia to RGB-14-P did not have any impact on incidence of fragility fractures.

GCP aspects

Audit certificates have been provided.

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

GCP aspects

Audit certificates have been provided.

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

2.5.7. Conclusions on the clinical efficacy

In study RGB-14-101, the efficacy analysis was based on the primary efficacy endpoint %CFB in lumbar spine BMD after 52 weeks. The primary efficacy analysis revealed that the difference between the RGB-14-P and the US-Prolia group was 0.34% (95% CI: -0.402, 1.090). Thus, the 95% CI was contained within the predefined margin of [-1.45, 1.45], supporting the claim of biosimilarity. Furthermore, AUEC of %CfB sCTX0-m6 until Week 26 has been addressed to as co-primary endpoint. Results showed that point estimate of geometric means and corresponding 95% CI of the ratio (RGB-14-P/US-Prolia) was contained within the 80% to 125% equivalence margin, supporting the claim of biosimilarity.

All sensitivity analyses confirmed the robustness of the results of the primary endpoint analysis.

The secondary efficacy analysis of %CfB BMD of vertebral (Lumbar spine) and non-vertebral (Total Hip and Femoral Neck) structures did not reveal clinically remarkable difference between RGB-14-P and RP and showed similar improvement in BMD of all vertebral and non-vertebral structures over time (Week 26 to Week 52) being supportive for the primary endpoint outcome.

However, the applicant should address the outstanding issues before a final conclusion of biosimilarity for RGB-14-P against US-licensed Prolia based on the submitted efficacy data can be made.

2.5.8. Clinical safety

RGB-14-P and RGB-14-X are investigational medicinal products intended to be biosimilars to Prolia and Xgeva, respectively. The active pharmaceutical ingredient in RGB-14-P and RGB-14-X is denosumab. The project code for the proposed biosimilar denosumab drug substance (DS) is RGB-14, while the project codes for the proposed biosimilar drug products (DP) of Prolia and Xgeva are RGB-14-P and RGB-14-X, respectively.

RGB-14-P contains the same amount and concentration of drug substance as the reference medicinal product, Prolia, and is supplied in a single-dose prefilled syringe ([PFS] 1 mL of a 60 mg/mL solution).

RGB-14-X contains the same amount and concentration of drug substance as the reference medicinal product, Xgeva, and is supplied in a single-dose vial (120 mg/1.7 mL in one vial).

Both RGB-14-P and RGB-14-X are administered as subcutaneous (sc) injections.

The safety of RGB-14-P/ RGB-14-X has been evaluated in two clinical studies: Study RGB-14-001 in healthy male volunteers (RGB-14-X versus US-sourced Xgeva) and study RGB-14-101 in women with postmenopausal osteoporosis (RGB-14-P versus US-sourced Prolia).

Study RGB-14-001 was a randomised, double-blind, single 60 mg fixed dose, parallel comparative pharmacokinetic and pharmacodynamic Phase I study comparing RGB-14-X versus US-Xgeva in healthy male subjects. The study was conducted at 3 different sites: Site1 in the UK, and Site 2 and 3 in Germany.

Study RGB-14-101 was a randomised, double-blind, multicenter Phase III study to assess the efficacy and safety of RGB-14-P compared to US-Prolia in female patients with postmenopausal osteoporosis (PMO). Study treatment was administered at a dose of 60 mg every 6 months, which is the approved dose and regimen. The study consisted of a Main Period (52 weeks) with 2 denosumab doses administered, and of a Transition period (26 weeks) with a third denosumab dose administered. The study was conducted in Poland, Bulgaria, Hungary, Czech Republic, Spain, Italy, the Ukraine and the USA. Data from the Main Period have been

submitted with the initial submission package; however, safety data from the Transition period were submitted by the applicant during the procedure.

Safety and tolerability were investigated in the safety analysis set (SAF). In study RGB-14-101 the SAF comprised 473 women, and in study RGB-14-001 the SAF comprised 165 healthy male volunteers.

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

Safety data collection

In both studies safety and tolerability endpoints included monitoring and recording of AE (including SAE), clinical laboratory test results (haematology, coagulation, serum chemistry, and urinalysis), vital sign measurements, 12-lead ECG results, and targeted physical examination findings.

All adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 26.0.

The safety profile of Amgen's denosumab is well established (Prolia SmPC, Prolia USPI, Xgeva SmPC, and Xgeva USPI). To account for the important known risks of hypocalcaemia and ONJ, special precautions were taken in both clinical studies.

The Prolia and Xgeva labels recommend correction of pre-existing hypocalcaemia 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 accordance with the label recommendations, the following measures were taken in both studies:

- Subjects with hypocalcaemia or vitamin D deficiency were excluded from study participation.
- Subjects received supplementation with calcium and vitamin D of at least:
- Study -001: 1000 mg/day calcium and 800 IU/day vitamin D3 from Screening to EOS
- Study -101: 1000 mg/day calcium and 800 IU/day vitamin D from Day 1 to EOS
- Monitoring of calcium levels was done at regular intervals.

Both studies also excluded subjects with a history or presence of ONJ or risk factors for ONJ. Subjects with active dental or jaw condition that required oral surgery or those with planned invasive dental procedure were also excluded from both studies.

No pooling of safety data was performed, as study -001 was conducted in healthy male subjects and study -101 in female subjects with PMO.

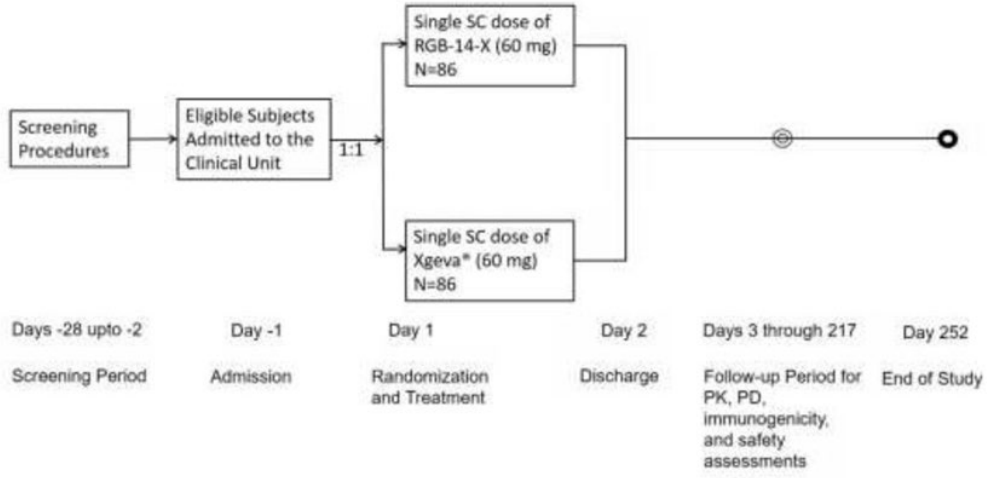
2.5.8.1. Patient exposure

Study RGB-14-001:

Healthy male subjects received a single sc injection of either 60 mg RGB-14-X or US-sourced Xgeva. Dose adjustments were not allowed and did not occur. The total duration of study participation for each participant in the study was 40 weeks.

The study consisted of a Screening period (up to 28 days), in-house treatment period (2 days), and a follow-up period (250 days). It was initially planned to enrol 172 subjects. Finally, 165 subjects were enrolled, due to the expiry of the US-Xgeva batch, to avoid further variability that might be introduced by using a second batch of the reference product.

Figure 14: Study Design of study RGB-14-001



Abbreviations: SC: subcutaneous; PD: pharmacodynamic; PK: pharmacokinetic.

Extent of exposure

All randomised participant received the assigned study drug (i.e. single dose of 60 mg denosumab); therefore, the SAF consisted of all 165 treated subjects (RGB-14-X: 83 subjects; US-Xgeva: 82 subjects).

Subject disposition

Of the 609 participants screened, 165 participants were randomised (103 in Site1, 26 in Site2, and 36 in Site3).

Participant disposition by site, treatment and overall (Screened Population) is presented below.

Table 57: Participant Disposition by Site, Treatment and Overall

Category	Site1		Site2		Site3		
	RGB-14-X 60 mg (N = 52) n (%)	US-sourced Xgeva® 60 mg (N = 51) n (%)	RGB-14-X 60 mg (N = 13) n (%)	US-sourced Xgeva® 60 mg (N = 13) n (%)	RGB-14-X 60 mg (N = 18) n (%)	US-sourced Xgeva® 60 mg (N = 18) n (%)	Overall (N = 165) n (%)
Subjects screened#							598*
Sites							
Site1							438
Site2							66
Site3							94
Screen failures#							433
Sites							
Site1							335
Site2							40
Site3							58
Subjects randomised	52 (100)	51 (100)	13 (100)	13 (100)	18 (100)	18 (100)	165 (100)
Subjects who received treatment	52 (100)	51 (100)	13 (100)	13 (100)	18 (100)	18 (100)	165 (100)
Subjects who did not receive treatment	0	0	0	0	0	0	0
Subjects who discontinued treatment	1 (1.9)	0	0	0	1 (5.6)	1 (5.6)	3 (1.8)
Subjects who completed study	51 (98.1)	51 (100)	13 (100)	13 (100)	17 (94.4)	17 (94.4)	162 (98.2)
Subjects withdrawn from study	1 (1.9)	0	0	0	1 (5.6)	1 (5.6)	3 (1.8)
Adverse event	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0
Initiated prohibited medication	0	0	0	0	0	0	0

Lost to follow-up	0	0	0	0	0	0	0
Physician decision	0	0	0	0	1 (5.6)	0	1 (0.6)
Protocol violation	0	0	0	0	0	0	0
Study terminated by Sponsor	0	0	0	0	0	0	0
Withdrawal by subject	1 (1.9)	0	0	0	0	0	1 (0.6)
Other	0	0	0	0	0	1 (5.6)	1 (0.6)
Other specify							
Parallel participation another study	0	0	0	0	0	1 (5.6)	1 (0.6)

* Note: In total, 609 subjects were screened for the study, however, data for 11 subjects who failed screening at Site1 EPCU were inadvertently missed to be included in the EDC (Refer to quality incident No.2 in Table 6.) Hence, data for these 11 subjects are not reflected in Table 14.1.1 and Listing 16.2.1.2. The Site1 Screening numbers for these subjects are: [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted].

N = number of subjects in randomised population in specific treatment or overall; n = number of subjects in each category in respective treatment, overall, in randomised population; % = (n/N)*100.

Abbreviations: EDC = Electronic Data Captured, EPCU = Early Phase Clinical Unit, UK = United Kingdom; US = United States.

n is based on Screened Population.

Source: Table 14.1.1

All 165 participants were compliant with treatment and received the planned single dose of either of the study drugs.

Overall, 162 (98.2%) participants completed the study. Three participants (1.8%) discontinued from the study due to the following reasons:

• One participant (RGB-14-X arm) was withdrawn from the study due to physician decision and the EOS visit was on Day 28.

• One participant (RGB-14-X arm) withdrew from the study for personal reasons. The EOS visit was on Day 148.

• One participant (US-sourced Xgeva) was withdrawn from the study due to physician decision and the EOS visit was on Day 62.

There were no discontinuations from the study due to AE.

Demographics and baseline characteristics

The study included male participants with a mean age (SD) of 39.4 (7.69) years. The majority of participants (77.6%) were of White race. Most participants (93.9%) were Not Hispanic or Latino by ethnicity. The demographic characteristics were generally well balanced between the test and reference treatment groups.

One participant had a major deviation related to inclusion/exclusion criteria.

All subjects were included in the SAF.

Concomitant medications or treatments

The frequency and pattern of use of concomitant medications (i.e., taken after start of study treatment) were similar across the treatment arms (RGB-14-X, US-Xgeva) in study RGB-14-001. The most frequently reported concomitant medications were mineral supplements and vitamins followed by vaccines against SARS-CoV-2.

Study RGB-14-101:

This was a randomised, double blind, multicentre, multiple fixed dose, two arm parallel group study to assess the efficacy, PD, safety, tolerability, and immunogenicity of RGB-14-P compared with US-licensed Prolia in participants with postmenopausal osteoporosis.

This study consisted of an up to 35-day Screening Period followed by the Main Period and followed by a Transition Period as described below:

• Main Period: The Main Period (52 weeks) consisted of Treatment Period 1 (26 weeks) and Treatment Period 2 (26 weeks). On Day 1 of Treatment Period 1, prior to dosing, the 473 participants were randomised in a 1:1 ratio to receive either RGB-14-P (n=242) or US-Prolia (n=231). The IMP was administered on two occasions in a double-blinded manner, on Day 1 of both Treatment Periods 1 and 2 (Weeks 0 and 26).

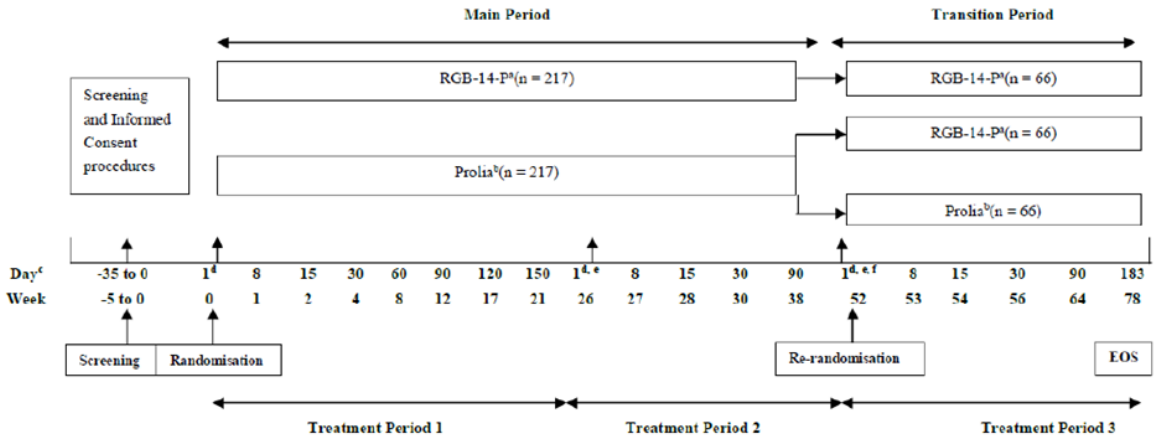
• Transition Period: The Transition Period consisted of Treatment Period 3 (26 weeks); the Transition Period was applicable to a subset of participants. On Day 1 of TP 3 (Week 52) a total of approximately 198 participants were planned to enter the TP. A subset of approximately 132 participants continuing in the Transition Period who received Prolia during the Main Period were to be re-randomised (1:1) to receive either a dose of RGB-14-P or Prolia in a double-blinded manner. A subset of approximately 66 participants continuing in the TP who received RGB-14-P during the Main Period would continue to receive a dose of RGB-14-P but would also follow the randomisation procedure to maintain blinding.

The end of the study was defined as the date of the last scheduled procedure shown in the schedule of assessments (SoA) for the last participant in the study.

The estimated duration of the clinical phase for participants in the Main Period from the Screening to the End-of-Study (EOS) Visit was approximately 13 months and for participants continuing in the Transition Period from the Screening Period until the EOS Visit was approximately 19 months.

The safety analysis set consisted of all participants dosed (473 subjects [100%]).

Figure 15: Study Design of study RGB-14-101 – Main and Transition Period



Abbreviations: EOS = End-of-Study; n = number of participants.

a. Test product.
b. Reference product.
c. Day(s) refer to days within Screening or Treatment Period
d. Dosing Visits.
e. Day 1 of Treatment Periods 2 and 3 is also Day 183 of the preceding Treatment Period.
f. Participants continuing to the Transition Period who previously received Prolia during the Main Period were re-randomised 1:1 to either receive RGB-14-P or Prolia in a double-blinded manner. Participants continuing to the Transition Period who received RGB-14-P during the Main Period continued to receive a dose of RGB-14-P but also followed the randomisation procedure to maintain blinding.

Extent of exposure

Of the 473 participants (242 in the RGB-14-P arm and 231 in the US-Prolia arm) who were randomised, all received the first injection of RGB-14-P or Prolia, and 446 (227 [93.8%] in the RGB-14-P group and 219 [94.8%] in the Prolia group) received the second injection of RGB-14-P or Prolia. A total of 27 (5.7%) participants (15 [6.2%] in the RGB-14-P group and 12 [5.2%] in the Prolia group) did not receive the second injection mainly due to reasons such as withdrawal by participant, AE and lost to follow-up.

Similar proportions of subjects in both treatment groups received both scheduled sc doses of 60 mg RGB-14-P or US-Prolia in the Main Period. Thus, the duration of exposure was comparable between treatment groups.

Table 58: Exposure – Main Period (Full Analysis Set for Main Period)

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
First injection not received	n (%)	0	0	0
First injection received	n (%)	242 (100)	231 (100)	473 (100)
Full dose	n (%)	242 (100)	231 (100)	473 (100)
Partial dose	n (%)	0	0	0
Second injection not received	n (%)	15 (6.2)	12 (5.2)	27 (5.7)
Second injection received	n (%)	227 (93.8)	219 (94.8)	446 (94.3)
Full dose	n (%)	227 (93.8)	219 (94.8)	446 (94.3)
Partial dose	n (%)	0	0	0

Abbreviations: N = number of subjects in the analysis set; n = number of subjects in the specific category.

%: calculated using the number of subjects in the analysis set as the denominator (n/N*100).

Source: Table 14.1.8.1

Subject disposition

Of the 1211 participants screened, 473 participants were randomised (242 in the RGB-14-P arm and 231 in the US-Prolia arm).

All randomised participants received the IMP, and 436 (92.2%) participants completed the Main Period of the study.

The percentage of participants who completed the Main Period was comparable between the two treatment arms (RGB-14-P: 225 [93%] participants, and US-Prolia: 211 [91.3%] participants).

The most common primary reason for study discontinuation in the Main Period was withdrawal by subject (23 [4.9%] participants – 8 patients (3.3%) in the RGB-14-P arm and 15 patients (6.5%) in the US-Prolia arm.

Overall, 4 (0.8%) participants discontinued the study due to an AE (2 in each study arm) and one (overall, 0.2%) participant in the US-Prolia arm discontinued the study due to death.

It is stressed by the applicant that the geopolitical conflict posed significant challenges to the conduct of the study in Ukraine. The sponsor terminated the study in Ukraine because IMP shipment and blood sample shipment to the Central Laboratory could not be ensured. The continuation of the treatment was decided on a case-by-case basis considering the ever-prevailing circumstances. The reason for end of treatment was not reported for three participants in Ukraine due to the war.

Table 59: Subject Disposition – Main Period (Enrolled Analysis Set)

Enrolled Analysis Set				1211
Screen Failures				738
Subject Randomised (Full Analysis Set)	n (%)	242 (100)	231 (100)	473 (100)
Subjects Dosed (Safety Analysis Set)	n (%)	242 (100)	231 (100)	473 (100)
Pharmacodynamic Analysis Set	n (%)	241 (99.6)	229 (99.1)	470 (99.4)
Immunogenicity Analysis Set	n (%)	239 (98.8)	228 (98.7)	467 (98.7)
Per Protocol Analysis Set	n (%)	240 (99.2)	229 (99.1)	469 (99.2)
Subjects Completed	n (%)	225 (93.0)	211 (91.3)	436 (92.2)
Treatment Policy Estimand	n (%)	242 (100)	231 (100)	473 (100)
Principal Stratum Estimand	n (%)	216 (89.3)	206 (89.2)	422 (89.2)
Randomised Subjects Withdrawn in the Main Period	n (%)	17 (7.0)	20 (8.7)	37 (7.8)
Reason for End of Treatment*				
Withdrawal by Subject	n (%)	8 (3.3)	13 (5.6)	21 (4.4)
Adverse Event	n (%)	2 (0.8)	2 (0.9)	4 (0.8)
Lost to Follow-up	n (%)	3 (1.2)	0	3 (0.6)
Death	n (%)	0	1 (0.4)	1 (0.2)
Protocol Deviation	n (%)	1 (0.4)	0	1 (0.2)
Other	n (%)	2 (0.8)	2 (0.9)	4 (0.8)
Other: An Exclusion Criterium has Been Found - More Than Three Years of Cumulative Use of Oral Bisphosphonates Prior the Screening Period.	n (%)	1 (0.4)	0	1 (0.2)
Other: Study Objective Confounded by Monoclonal Gammopathy	n (%)	1 (0.4)	0	1 (0.2)
Other: Subject's Personal Reason	n (%)	0	1 (0.4)	1 (0.2)
Other: The Patient for a Personal Reason Cannot Attend an Appointment for Too Long	n (%)	0	1 (0.4)	1 (0.2)
Reason for End of Study				

Completed	n (%)	162 (66.9)	86 (37.2)	248 (52.4)
Withdrawal by Subject	n (%)	8 (3.3)	15 (6.5)	23 (4.9)
Adverse Event	n (%)	2 (0.8)	2 (0.9)	4 (0.8)
Lost to Follow-up	n (%)	3 (1.2)	0	3 (0.6)
Study Terminated by Sponsor	n (%)	1 (0.4)	1 (0.4)	2 (0.4)
Death	n (%)	0	1 (0.4)	1 (0.2)
Inclusion/Exclusion Criteria Not Met	n (%)	1 (0.4)	0	1 (0.2)
Protocol Deviation	n (%)	1 (0.4)	0	1 (0.2)

Abbreviations: eCRF = electronic case report form; N = number of subjects with each treatment, for the overall study group it is the number of subjects in the Enrolled Analysis Set; n = number of subjects in specific category.

%: calculated using the number of subjects with each treatment, or the Enrolled Analysis Set for the overall study group, as denominator (n/N*100).

*Reason for end of Treatment was not reported for patients [redacted], [redacted] and [redacted]. Number of subjects who completed Main Period, did not match with number of completed in end of study as a portion of patients continued in the Transition Period and did not complete end of study page in eCRF while in Main Period.

Source: Table 14.1.1.1

Demographics and baseline characteristics

The study included postmenopausal women with a diagnosis of osteoporosis with a mean age (SD) of 66.7 (5.06) years. Most participants (99.4%) were White and were Not Hispanic or Latino (91.3%) by ethnicity. The demographic characteristics were comparable between the RGB-14-P and the Prolia treatment arms.

Table 60: Subject Demographics – Main Period (FAS)

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Age (years)	n	242	231	473
	Mean	66.7	66.8	66.7
	SD	5.20	4.91	5.06
	Median	66.0	66.0	66.0
	Minimum	60	60	60
	Maximum	83	84	84
Gender				
Female	n (%)	242 (100)	231 (100)	473 (100)
Osteoporosis diagnosis				

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Subjects with prior osteoporosis diagnosis	n (%)	188 (77.7)	163 (70.6)	351 (74.2)
Subjects with new osteoporosis diagnosis	n (%)	54 (22.3)	68 (29.4)	122 (25.8)
Ethnic Origin				
Hispanic or Latino	n (%)	18 (7.4)	22 (9.5)	40 (8.5)
Not Hispanic or Latino	n (%)	223 (92.1)	209 (90.5)	432 (91.3)
Not Reported	n (%)	1 (0.4)	0	1 (0.2)
Race				
White	n (%)	241 (99.6)	229 (99.1)	470 (99.4)
Black or African American	n (%)	0	2 (0.9)	2 (0.4)
Native Hawaiian or Other Pacific Islander	n (%)	1 (0.4)	0	1 (0.2)
Height (cm)	n	242	231	473
	Mean	159.153	159.278	159.214
	SD	5.8416	6.6719	6.2545
	Median	159.000	160.000	159.000
	Minimum	143.50	139.00	139.00
	Maximum	179.80	176.70	179.80
Weight (kg)	n	242	231	473
	Mean	63.99	65.05	64.51
	SD	9.695	8.953	9.345
	Median	63.00	64.50	64.00
	Minimum	50.0	50.0	50.0
	Maximum	90.0	89.7	90.0
BMI (kg/m^2)	n	242	231	473
	Mean	25.249	25.714	25.476
	SD	3.4772	3.7615	3.6225
	Median	24.795	25.390	25.070

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
	Minimum	18.07	18.42	18.07
	Maximum	36.46	37.80	37.80
Country				
United States of America	n (%)	11 (4.5)	9 (3.9)	20 (4.2)
Spain	n (%)	13 (5.4)	22 (9.5)	35 (7.4)
Bulgaria	n (%)	40 (16.5)	27 (11.7)	67 (14.2)
Hungary	n (%)	19 (7.9)	20 (8.7)	39 (8.2)
Ukraine	n (%)	1 (0.4)	2 (0.9)	3 (0.6)
Italy	n (%)	8 (3.3)	15 (6.5)	23 (4.9)
Czechia	n (%)	25 (10.3)	36 (15.6)	61 (12.9)
Poland	n (%)	125 (51.7)	100 (43.3)	225 (47.6)

Abbreviations: BMI = body mass index; N = number of subjects in the analysis set; n = number of subjects in the specific category; SD = standard deviation.

%: calculated using the number of subjects in the analysis set as the denominator (n/N*100).

Source: Table 14.1.3.1

Disease characteristics

Baseline disease-specific characteristics such as BMD, T-score, P1nP and sCTX values were balanced between the treatment arms.

Medical and surgical history reported were comparable between the RGP-14-P and US-Prolia treatment arms.

Concomitant medications or treatments

The frequency and pattern of concomitant medications reported were comparable between the RGB-14-P and US-Prolia treatment arms in study RGB-14-101. The most frequently reported concomitant medications were mineral supplements and vitamins followed by HMG-CoA reductase inhibitors, beta blocking agents and thyroid hormones.

2.5.8.2. Adverse events

Study RGB-14-001:

Overall, 128 (77.6%) participants in the Safety Population reported 424 TEAE (n=62 subjects [74.7%] with 211 events in the RGB-14-X-arm versus n=66 subjects [80.5%] with 213 events in the Xgeva arm, respectively).

Most participants reported TEAE that were mild or moderate in intensity. Three (1.8%) participants reported 4 TEAE that were severe in intensity: 1 event of influenza in 1 patient of the RGB-14-X arm; 1 event of nerve compression in 1 participant, and 2 events of meniscus injury and subsequent arthroscopy (procedure) in another participant of the US-Xgeva arm. These events were considered not related to the study drug.

Table 61: TEAE Overview by Treatment and Overall

Adverse Event Category	RGB-14-X 60 mg (N = 83) n (%) E	US-sourced Xgeva® 60 mg (N = 82) n (%) E	Overall (N = 165) n (%) E
Any TEAE	62 (74.7) 211	66 (80.5) 213	128 (77.6) 424
Any serious TEAE	1 (1.2) 1	1 (1.2) 1	2 (1.2) 2
Serious TEAE outcome of death	0	0	0
TEAE leading to study discontinuation	0	0	0
Serious TEAE related study treatment	0	0	0
Serious TEAE leading to study discontinuation	0	0	0
Serious TEAE related study treatment leading to discontinuation	0	0	0
Serious TEAE related study treatment leading to death	0	0	0
Injection site reaction	2 (2.4) 2	2 (2.4) 2	4 (2.4) 4
TEAE by worst severity			
Mild	30 (36.1) 151	27 (32.9) 147	57 (34.5) 298
Moderate	31 (37.3) 59	37 (45.1) 63	68 (41.2) 122
Severe	1 (1.2) 1	2 (2.4) 3	3 (1.8) 4
Life-threatening	0	0	0
Death	0	0	0
Adverse Event Category	**RGB-14-X 60 mg (N = 83) n (%) E**	**US-sourced Xgeva® 60 mg (N = 82) n (%) E**	**Overall (N = 165) n (%) E**
TEAE by worst causality			
Yes	25 (30.1) 45	25 (30.5) 40	50 (30.3) 85
No	37 (44.6) 166	41 (50.0) 173	78 (47.3) 339

N = number of subjects in Safety Population in respective treatment or overall; E = number of TEAE in the category in respective treatment or overall, in the Safety Population; n = number of subjects with at least 1 TEAE in the category in respective treatment or overall, in the Safety Population.

Subjects with multiple events in the same category were counted only once in that category.

If a subject had multiple events with different severity, number of events (E) was counted per severity while the subject was counted only once at worst severity toward the number of subject (n).

If a subject had multiple events with different causality, number of events (E) was counted per causality while the subject was counted only once at worst causality toward the number of subject (n).

Abbreviations: TEAE = treatment-emergent adverse event; US = United States.

Source: Table 14.3.1.1, Listing 16.2.7.10

Common TEAE by SOC & PT:

Overall, TEAE were most frequently reported in the SOC of Infections and infestations (45.5%), Nervous system disorders (26.1%), and Gastrointestinal disorders and General disorders and administration site conditions (23.6%, each).

• TEAE in the SOC of Infections and infestations were reported by 48.2% in RGB-14-X group versus 42.7% in Xgeva group.

• TEAE in the SOC of Nervous system disorders were reported by 25.3% in RGB-14-X group versus 26.8% in Xgeva group.

• TEAE in the SOC of Gastrointestinal disorders were reported by 24.1% in RGB-14-X group versus 23.2% in Xgeva group.

• TEAE in the SOC of General disorders and administration site conditions were reported by 21.7% in RGB-14-X group versus 25.6% in Xgeva group.

The most frequently reported TEAE by PT were nasopharyngitis (21.8% participants), COVID-19 (20.0% participants), and headache (15.2% participants).

Nasopharyngitis was reported by 21.7% versus 22.0% participants in the RGB-14-X and Xgeva arms, respectively. COVID-19 was reported by 20.5% versus 19.5% participants in the RGB-14-X and Xgeva arms, respectively. Headache was reported by 14.5% versus 15.9% participants in the RGB-14-X and Xgeva arms, respectively.

Overall, frequencies and pattern of TEAE were comparable between the treatment arms.

Adverse drug reactions

Overall, TEAE considered related to the study drug were reported by 50 participants (30.3%; RGB-14-X: 30.1% versus US-Xgeva: 30.5%, respectively); TEAE that were considered not related to study drug were reported by 78 participants (47.3%).

TEAE considered related to the study drug reported in at least 3% participants in any treatment group were dizziness postural (5.5% participants, overall), headache (4.2% participants, overall), fatigue (3.0% participants, overall), and back pain (1.8%, overall).

Dizziness postural was reported by 6.0% participants in the RGB-14-X arm versus 4.9% participants in the Xgeva arm. Headache was reported by 4.8% participants in the RGB-14-X arm versus 3.7% of participants in the Xgeva arm. Fatigue was reported by 3.6% participants in the RGB-14-X arm versus 2.4% participants in the Xgeva arm.

Back pain was reported by 3.6% participants in the RGB-14-X arm versus 0% participants in the Xgeva arm. These events were mild in intensity with an onset on Day 1 or Day 2 and resolved within 1-4 days of onset.

Table 62: TEAE Related to Study Treatment in ⩾3% of Participants by SOC and PT, Treatment and Overall

System Organ Class Preferred Term	RGB-14-X 60 mg (N = 83) n (%) E	US-sourced Xgeva® 60 mg (N = 82) n (%) E	Overall (N = 165) n (%) E
Any TEAE Related to Study Treatment in ≥ 3 of Subjects by System Organ Class and Preferred Term	15 (18.1) 21	9 (11.0) 13	24 (14.5) 34
General disorders and administration site conditions			
Any Event	3 (3.6) 4	2 (2.4) 2	5 (3.0) 6
Fatigue	3 (3.6) 4	2 (2.4) 2	5 (3.0) 6
Musculoskeletal and connective tissue disorders			
Any Event	3 (3.6) 3	0	3 (1.8) 3
Back pain	3 (3.6) 3	0	3 (1.8) 3
Nervous system disorders			
Any Event	9 (10.8) 14	7 (8.5) 11	16 (9.7) 25
Dizziness postural	5 (6.0) 7	4 (4.9) 5	9 (5.5) 12
Headache	4 (4.8) 7	3 (3.7) 6	7 (4.2) 13

N = number of subjects in Safety Population in respective treatment or overall; E = number of TEAE related to study treatment in the category in respective treatment or overall, in Safety Population; n = number of subjects with at least 1 TEAE related to study treatment in the category in respective treatment or overall, in Safety Population.

Adverse events are coded to SOC and PT using MedDRA version 26.0.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Affairs; PT = Preferred Term, SOC = System Organ Class; TEAE = treatment-emergent adverse event; US = United States.

Source: Table 14.3.1.7

It is stated that most participants reported TEAEs that were mild or moderate in intensity.

Injection site reactions

Injection site reaction was reported by 4 participants (2 in each treatment group). The keywords for injection site reactions included a variety of local reactions to the IMP injection (e.g., swelling, erythema, etc) and was not limited to the preferred term "injection site reaction".

Study RGB-14-101:

In the Phase III study in female PMO patients, 65.5% (310/473) of participants experienced at least one TEAE during the Main Period of 52 weeks. The percentage of participants experiencing at least one TEAE was similar in the two treatment arms (RGB-14-P arm: 65.3% [158/242]; US-Prolia arm: 65.8% [152/231]).

The majority of TEAE (97.9%) reported during the Main Period were mild or moderate in intensity. The percentage of participants reporting at least one severe TEAE was similar in the two treatment arms (RGB-14-P arm: 3.3% [8/242]; Prolia arm: 3.5% [8/231]).

Only one of all severe TEAE, namely the TEAE of osteitis, reported by 1 (0.4%) participant in the RGB-14-P group, was considered related by the Investigator and led to subject discontinuation from the study. This osteitis event reported in the RGB-14-P group was, however, non-serious.

Overall, 5.7% (27/473) of participants experienced at least one fracture TEAE during the Main Period. A higher percentage of participants in the Prolia arm than in the RGB-14-P arm experienced at least one fracture TEAE (7.8% [18/231] vs 3.7% [9/242], respectively).

One participant in the Prolia group experienced a TEAE leading to death. There were no TEAE leading to death in the RGB-14-P group.

Table 63: Summary of Adverse Events – Main Period

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Any AEs	n (%) E	161 (66.5) 556	158 (68.4) 463	319 (67.4) 1019
Any TEAEs	n (%) E	158 (65.3) 515	152 (65.8) 438	310 (65.5) 953
Any TEAEs severe or worse severity	n (%) E	8 (3.3) 8	9 (3.9) 12	17 (3.6) 20
Severe	n (%) E	8 (3.3) 8	8 (3.5) 11	16 (3.4) 19
Life-threatening	n (%) E	0	0	0
Fatal	n (%) E	0	1 (0.4) 1	1 (0.2) 1
Any treatment related TEAE	n (%) E	36 (14.9) 72	32 (13.9) 47	68 (14.4) 119
Any treatment related TEAE severe or worse severity	n (%) E	1 (0.4) 1	0	1 (0.2) 1
Severe	n (%) E	1 (0.4) 1	0	1 (0.2) 1
Life-threatening	n (%) E	0	0	0
Fatal	n (%) E	0	0	0
Any serious TEAEs	n (%) E	7 (2.9) 9	16 (6.9) 21	23 (4.9) 30
Any serious TEAEs severe or worse severity	n (%) E	5 (2.1) 5	9 (3.9) 12	14 (3.0) 17
Severe	n (%) E	5 (2.1) 5	8 (3.5) 11	13 (2.7) 16
Life-threatening	n (%) E	0	0	0
Fatal	n (%) E	0	1 (0.4) 1	1 (0.2) 1
Any treatment related serious TEAE	n (%) E	0	0	0
Any treatment related serious TEAE severe or worse severity	n (%) E	0	0	0
Severe	n (%) E	0	0	0
Life-threatening	n (%) E	0	0	0
Fatal	n (%) E	0	0	0
Any non-serious TEAEs	n (%) E	158 (65.3) 506	149 (64.5) 417	307 (64.9) 923
Any AEs leading to subject discontinuation	n (%) E	2 (0.8) 2	3 (1.3) 3	5 (1.1) 5
Any TEAEs leading to subject discontinuation	n (%) E	2 (0.8) 2	3 (1.3) 3	5 (1.1) 5

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Any treatment related TEAE leading to subject discontinuation	n (%) E	1 (0.4) 1	0	1 (0.2) 1
Any TEAEs leading to discontinuation of IMP	n (%) E	2 (0.8) 2	2 (0.9) 2	4 (0.8) 4
Any treatment related TEAE leading to discontinuation of IMP	n (%) E	1 (0.4) 1	0	1 (0.2) 1
Any fracture TEAE	n (%) E	9 (3.7) 12	18 (7.8) 20	27 (5.7) 32
Any fracture TEAE severe or worse severity	n (%) E	2 (0.8) 2	1 (0.4) 1	3 (0.6) 3
Severe	n (%) E	2 (0.8) 2	1 (0.4) 1	3 (0.6) 3
Life-threatening	n (%) E	0	0	0
Fatal	n (%) E	0	0	0
Any treatment related fracture TEAE	n (%) E	0	0	0
Any treatment related fracture TEAE severe or worse severity	n (%) E	0	0	0
Severe	n (%) E	0	0	0
Life-threatening	n (%) E	0	0	0
Fatal	n (%) E	0	0	0
Any serious fracture TEAEs	n (%) E	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Any serious fracture TEAEs severe or worse severity	n (%) E	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Severe	n (%) E	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Life-threatening	n (%) E	0	0	0
Fatal	n (%) E	0	0	0
Any treatment related serious fracture TEAE	n (%) E	0	0	0
Any treatment related serious fracture TEAE severe or worse severity	n (%) E	0	0	0
Severe	n (%) E	0	0	0
Life-threatening	n (%) E	0	0	0
Fatal	n (%) E	0	0	0
Deaths	n (%) E	0	1 (0.4) 1	1 (0.2) 1
Any AE leading to death	n (%) E	0	1 (0.4) 1	1 (0.2) 1
Any TEAE leading to death	n (%) E	0	1 (0.4) 1	1 (0.2) 1
Any treatment related fatal serious TEAEs	n (%) E	0	0	0
Any injection site reactions	n (%) E	0	2 (0.9) 2	2 (0.4) 2

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Any injection site reactions severe or worse severity	n (%) E	0	0	0
Severe	n (%) E	0	0	0
Life-threatening	n (%) E	0	0	0
Fatal	n (%) E	0	0	0
Any injection site reactions of CTCAE grade ≥ 3	n (%) E	0	0	0

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; E = Number of events; IMP = Investigational Medicinal Product; N = Number of subjects dosed with each treatment (or any treatment as applicable); n = Number of subjects with characteristic; TEAE = treatment-emergent adverse event.

Notes: Only events observed during the Main Period are reported in this table.

%: Calculated using the number of subjects dosed with each treatment (or any treatment as applicable) as the denominator (n/N*100).

IMP is RGB-14-P or Prolia.

AE ID 5 for Subject [redacted] was recorded as humerus fracture since no alternative coding was identified for this AE; however, due to its nature (condition after fracture) it should not be considered as a fracture AE.

Subjects [redacted] and [redacted] had vertebral fractures detected on X-Ray by central reading but these were not reported as AEs by the Investigator. A protocol deviation was recorded for not reporting these AEs.

Source: Table 14.3.1.1.1

Common TEAE by SOC & PT:

TEAE were most frequently reported in the following SOCs with an incidence ≥10% in both treatment arms: Infections and infestations (RGB-14-P arm: 39.3%; Prolia arm: 38.5%), Musculoskeletal and connective tissue disorders (RGB-14-P arm: 16.1%; Prolia arm: 14.3%), Metabolism and nutrition disorders (RGB-14-P arm: 14.9%; Prolia arm: 14.3%) and gastrointestinal disorders (RGB-14-P arm: 13.2%; Prolia arm: 11.3%).

The most frequently reported TEAE (incidence ≥5%) by PT in the RGB-14-P arm were COVID-19 (9.9%), nasopharyngitis and upper respiratory tract infection (9.5% each), hypocalcaemia (9.1%), headache (5.4%) and arthralgia (5.0%); in the Prolia group COVID-19 (10.4%), hypocalcaemia (9.5%), nasopharyngitis (8.7%) and hypertension (5.6%) were most frequently reported.

Except for upper respiratory tract infection, which was reported at a higher incidence in the RGB-14-P group than in the Prolia group (9.5% vs 4.3%), the incidences of the other most frequently reported PTs were similar in the two treatment groups. None of the upper respiratory tract infections were reported as SAE.

Table 64: TEAE in ⩾3% of subjects in either treatment group by Treatment, SOC and PT

System Organ Class Preferred Term	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Any TEAEs in ≥ 3% of subjects in either treatment group	n (%) E	107 (44.2) 193	92 (39.8) 165	199 (42.1) 358
Infections and infestations				
COVID-19	n (%) E	24 (9.9) 24	24 (10.4) 25	48 (10.1) 49
Nasopharyngitis	n (%) E	23 (9.5) 29	20 (8.7) 27	43 (9.1) 56
Upper RTI	n (%) E	23 (9.5) 33	10 (4.3) 12	33 (7.0) 45
Urinary tract infection	n (%) E	11 (4.5) 12	11 (4.8) 17	22 (4.7) 29
Bronchitis	n (%) E	2 (0.8) 2	8 (3.5) 9	10 (2.1) 11
Metabolism and nutrition disorders				
Hypocalcemia	n (%) E	22 (9.1) 31	22 (9.5) 27	44 (9.3) 58
Musculoskeletal and connective tissue disorders				
Arthralgia	n (%) E	12 (5.0) 16	10 (4.3) 13	22 (4.7) 29
Back pain	n (%) E	4 (1.7) 4	9 (3.9) 9	13 (2.7) 13
Osteoarthritis	n (%) E	10 (4.1) 10	3 (1.3) 3	13 (2.7) 13
Vascular disorders				
Hypertension	n (%) E	7 (2.9) 8	13 (5.6) 14	20 (4.2) 22
Nervous system disorders				
Headache	n (%) E	13 (5.4) 14	4 (1.7) 5	17 (3.6) 19
Gastrointestinal disorders				
Diarrhea	n (%) E	8 (3.3) 10	4 (1.7) 4	12 (2.5) 14

*Abbreviations: E: Number of events; N: Number of subjects dosed with each treatment; n: Number of subjects with adverse event; %: Calculated using the number of subjects dosed with each treatment (or any treatment as applicable) as the denominator (n/N*100); RTI = Respiratory tract infection*

As stated above, during the Main Period, 9.5% of subjects (23/242) in the RGB-14-P arm and 4.3% of subjects (10/231) in the Prolia arm experienced at least one AE with the PT of Upper respiratory tract infection.

All these Upper respiratory tract infection AEs were of mild or moderate severity. None of these AEs resulted in the discontinuation of the study/study treatment or were assessed as SAEs. In the RGB-14-P arm, there were seven subjects (2.9%) who experienced two or more AEs with the PT of Upper respiratory tract infection, while in the Prolia arm there was one subject (0.4%) who had multiple Upper respiratory tract infection AEs.

AEs with the PT of Upper respiratory tract infection are summarised in the table below. The majority of subjects who had Upper respiratory tract infection AEs only experienced events that were considered by investigators as not related to the study treatment (RGB-14-P: 19 out of 23 subjects; Prolia: nine out of ten subjects). Most Upper respiratory tract infection ADRs were reported with moderate severity (RGB 14-P: 3 out of 4 subjects who had Upper respiratory tract infection ADR; Prolia: 1 subject who had an Upper respiratory tract infection ADR).

Upper respiratory tract infection AEs considered treatment-related were reported in four (1.7%) subjects in the RGB-14-P arm, which corresponds to the frequency of Upper respiratory tract infection ADR detailed in the Prolia EU Product Information (common frequency [≥ 1/100 to < 1/10]). In the Prolia arm, one (0.4%) subject experienced an Upper respiratory tract infection ADR.

Among the subjects who experienced ADRs with the PT of Upper respiratory tract infection, two out of the four subjects in the RGB 14-P arm and the one subject in the Prolia arm had other infectious ADRs reported. In the RGB-14-P arm, one subject had the additional infectious ADR of Urethritis, while another subject

experienced the ADRs of Urinary tract infection and Nasopharyngitis. In the Prolia arm, the subject who had an Upper respiratory tract infection ADR had an additional infectious ADR of Nasopharyngitis.

Table 65: Study RGB-14-101: Adverse events of the PT Upper respiratory tract infection by treatment arm, causality, system organ class and preferred term - Main Period (Safety Analysis Set)

System Organ Class Preferred Term	Causality	RGB-14-P N = 242 n (%)	Prolia N = 231 n (%)
Infections and infestations			
Upper respiratory tract infection	Any causality	23 (9.5)	10 (4.3)
	Related	4 (1.7)	1 (0.4)

n = number of subjects with at least one AE; N = number of subjects
*% = n/N*100*
Note: Adverse Events refer to Treatment Emergent Adverse Events (TEAEs)
If more than 1 AE was coded to the same preferred term for the same subject, the subject was counted only once for that preferred term (PT)
Source: Table 14.3.1.2.1, Table 14.3.1.5.1 RGB-14-101 CSR

Adverse events of COVID-19

Overall, 10.1% (48/473) of participants had at least one TEAE of COVID-19 infection. The percentage of participants was comparable between the RGB-14-P and Prolia arms (9.9% [24/242] and 10.4% [24/231], respectively). The COVID-19 infections reported in most participants in both treatment groups were mild in severity (6.2% [15/242] in the RGB-14-P arm and 6.9% [16/231] in the Prolia arm). None of the COVID-19 infections reported were severe or serious.

Except for 1 (0.4%) participant in the Prolia arm, none of the other participants experienced COVID-19 infections that were considered related to the study drug. None of the COVID-19 infections led to participant discontinuation from treatment or the study.

In addition to the COVID-19 infections reported, the non-serious TEAE of COVID-19 pneumonia and post-acute COVID-19 syndrome were reported by 1 (0.4%) participant each in the RGB-14-P arm. Both events were mild in severity and not considered to be related to the study drug. Neither of the events led to participant discontinuation from treatment or study.

Overall, frequencies and pattern of TEAE were comparable between the treatment arms.

Adverse drug reactions

Overall, 14.4% (68/473) of participants experienced at least one TEAE that was considered to be related to the IMP by the Investigator during the Main Period. The percentage of participants experiencing at least one TEAE considered to be related to the IMP was comparable between the two treatment arms (RGB-14-P arm: 14.9% [36/242]; Prolia arm: 13.9% [32/231]).

Hypocalcaemia was the most frequently reported TEAE that was considered related to study treatment; it was reported by a similar percentage of participants in the RGB-14-P and Prolia arms (6.6% and 6.9%, respectively).

Table 66: TEAE Related to Study Treatment in ⩾3% of Subjects by Treatment, SOC and PT – Main Period

System Organ Class Preferred Term	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Any treatment-related TEAEs in ≥ 3% of subjects in either treatment group	n (%) E	16 (6.6) 25	16 (6.9) 18	32 (6.8) 43
Metabolism and nutrition disorders				
Hypocalcaemia	n (%) E	16 (6.6) 25	16 (6.9) 18	32 (6.8) 43

Abbreviations: E = number of events; N = number of subjects dosed with each treatment; n = number of subjects with adverse event; TEAE = treatment-emergent adverse event.

Notes: Only events observed during the Main Period are reported in this table.

%: calculated using the number of subjects dosed with each treatment (or any treatment as applicable) as the denominator (n/N*100).

All adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.

Source: Table 14.3.1.31.1

Injection site reactions

Two participants in the Prolia arm experienced injection site reactions. By PT, these were injection site erythema and injection site rash; one TEAE for each of the two participants. The intensity of the TEAE was rated as mild. The events were considered by the investigator to be related to the IMP. None of the injection site reactions were severe or worse (i.e. ≥ Grade 3) in severity.

None of participants in the RGB-14-P arm experienced injection site reactions.

Table 67: Injection Site Reactions by Treatment, SOC and PT – Main Period

System Organ Class Preferred Term	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Any TEAEs	n (%) E	0	2 (0.9) 2	2 (0.4) 2
General disorders and administration site conditions	**n (%) E**	**0**	**2 (0.9) 2**	**2 (0.4) 2**
Injection site erythema	n (%) E	0	1 (0.4) 1	1 (0.2) 1
Injection site rash	n (%) E	0	1 (0.4) 1	1 (0.2) 1

System Organ Class Preferred Term	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)

Abbreviations: E = number of events; N = number of subjects dosed with each treatment; n = number of subjects with adverse event; TEAE = treatment-emergent adverse event.

Notes: Only events observed during the Main Period are reported in this table.

%: calculated using the number of subjects dosed with each treatment (or any treatment as applicable) as the denominator (n/N*100).

All adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.

Source: Table 14.3.1.27.1

2.5.8.3. Serious adverse event/deaths/other significant events

Study RGB-14-001:

AESI

No AE of special interest (AESI) have been defined by the applicant.

SAE

SAE were reported in two participants (1 event of nerve compression in the US-Xgeva arm and 1 event of influenza in the RGB-14-X arm) and were considered not related to the study drug. Both SAEs resolved, and the participants completed the study.

Narratives are provided in the RGB-14-001 CSR.

Deaths

No deaths were reported in the study.

Study RGB-14-101:

AESI

With the initial submission, no AESI have been defined by the applicant. However, fracture TEAE assessment was a secondary safety endpoint in the study protocol of study RGB-14-101 and was therefore presented as "other significant TEAE".

Overall, 5.7% (27/473) of participants experienced at least one fracture TEAE during the Main Period. Fracture TEAEs were more frequently reported in the Prolia arm (7.8% [18/231] with 20 events) than in the RGB-14-P arm (3.7% [9/242] with 12 events).

The most frequently reported fracture TEAEs (incidence ≥ 0.8%) in the RGB-14-P arm were foot fracture, lumbar vertebral fracture, and spinal compression fracture (2 [0.8%] participants and 2 events, each); and thoracic vertebral fracture (6 [2.6%] participants, 6 events), tooth fracture, and rib fracture (2 [0.9%] participants and 2 events, each) in the Prolia arm.

None of the fracture TEAE reported during the Main Period were considered to be related to the IMP.

Overall 0.6% (3/473) of participants experienced at least one fracture TEAE that was Grade 3 or worse in severity (2 [0.8%] participants in the RGB-14-P arm experiencing foot fracture and humerus fracture and 1

[0.4%] participant in the Prolia arm experiencing a radius fracture). None of them was considered related to the study drugs by the investigator.

Two (0.4%) participants experienced fracture SAE during the Main Period (1 participant each in the RGB-14-P and Prolia arms [0.4%]). By PT, the fracture SAE reported in the RGB-14-P group was humerus fracture; in the Prolia group it was radius fracture. The fracture SAEs reported in both participants were severe; they were not considered to be related to the study drugs.

Table 68: Study RGB-14-101: Fracture adverse events by treatment arm, severity, system organ class and preferred term – Main Period (Safety Analysis Set)

System Organ Class Preferred Term	RGB-14-P N=242						Prolia N=231					
	Mild/Moderate		Severe		Any severity		Mild/Moderate		Severe		Any severity	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects who had at least one fracture AE	**7**	**(2.9)**	**2**	**(0.8)**	**9**	**(3.7)**	**17**	**(7.4)**	**1**	**(0.4)**	**18**	**(7.8)**
Injury, poisoning and procedural complications	**7**	**(2.9)**	**2**	**(0.8)**	**9**	**(3.7)**	**16**	**(6.9)**	**1**	**(0.4)**	**17**	**(7.4)**
Foot fracture	1	(0.4)	1	(0.4)	2	(0.8)	1	(0.4)	0	(0)	1	(0.4)
Forearm fracture	0	(0)	0	(0)	0	(0)	1	(0.4)	0	(0)	1	(0.4)
Hand fracture	0	(0)	0	(0)	0	(0)	1	(0.4)	0	(0)	1	(0.4)
Humerus fracture	0	(0)	1	(0.4)	1	(0.4)	1	(0.4)	0	(0)	1	(0.4)
Lower limb fracture	0	(0)	0	(0)	0	(0)	1	(0.4)	0	(0)	1	(0.4)
Lumbar vertebral fracture	2	(0.8)	0	(0)	2	(0.8)	1	(0.4)	0	(0)	1	(0.4)
Radius fracture	0	(0)	0	(0)	0	(0)	0	(0)	1	(0.4)	0	(0.4)
Rib fracture	0	(0)	0	(0)	0	(0)	2	(0.9)	0	(0)	2	(0.9)
Spinal compression fracture	2	(0.8)	0	(0)	2	(0.8)	0	(0)	0	(0)	0	(0)
Thoracic vertebral fracture	1	(0.4)	0	(0)	1	(0.4)	6	(2.6)	0	(0)	6	(2.6)
Tooth fracture	1	(0.4)	0	(0)	1	(0.4)	2	(0.9)	0	(0)	2	(0.9)
Nervous system disorders	**0**	**(0)**	**0**	**(0)**	**0**	**(0)**	**1**	**(0.4)**	**0**	**(0)**	**1**	**(0.4)**
Spinal cord compression	0	(0)	0	(0)	0	(0)	1	(0.4)	0	(0)	1	(0.4)

AE = adverse event; n = number of subjects with at least one AE; N = number of subjects
*%=n/N*100*
Note: Adverse Events refer to Treatment Emergent Adverse Events (TEAEs)
If more than 1 AE was coded to the same preferred term (PT) for the same subject, the subject was counted only once for that preferred term.
If 1 PT was reported more than once with different severity for the same subject, the worst severity was counted for that PT.
If a subject had multiple events with different severity, then the subject was counted only once at the worst severity for the number of subjects (n).
For any AEs, severity was scored on a five-point scale as mild, moderate, severe, life threatening and death. The group mild/moderate includes AEs with mild and moderate severity; the group severe includes AEs with severity assessment of severe, life-threatening and death.
Source: Table 14.3.1.17.1, RGB-14-101 CSR

During the procedure, the applicant provided an appropriate list of AESI for their biosimilar product, reflecting the known risks for the originator Prolia, which are: hypocalcaemia, skin infection leading to hospitalisation, osteonecrosis of the jaw, hypersensitivity reactions, atypical femoral fracture, and hypercalcaemia in paediatric patients.

In addition, safety analyses have been provided for those AESI defined. No clinically meaningful differences were observed between the study arms.

SAE

Overall, 4.9% (23/473) of participants experienced at least one treatment-emergent SAE during the 52-Week Main Period. A higher percentage of participants in the Prolia arm than in the RGB-14-P arm experienced at least one SAE (6.9% [16/231] vs 2.9% [7/242], respectively).

Table 69: Treatment-emergent SAE by Treatment, SOC and PT – Main Period

System Organ Class Preferred Term	Statistic	RGB-14-P (N = 242)		Prolia (N = 231)		Overall Study (N = 473)	
Any TEAEs	n (%) E	7 (2.9)	9	16 (6.9)	21	23 (4.9)	30
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**n (%) E**	**1 (0.4)**	**1**	**6 (2.6)**	**6**	**7 (1.5)**	**7**
Bladder cancer	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Breast cancer	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Clear cell renal cell carcinoma	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Follicular lymphoma	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Invasive ductal breast carcinoma	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Renal neoplasm	n (%) E	0		1 (0.4)	1	1 (0.2)	1

System Organ Class Preferred Term	Statistic	RGB-14-P (N = 242)		Prolia (N = 231)		Overall Study (N = 473)	
Thyroid cancer	n (%) E	1 (0.4)	1	0		1 (0.2)	1
Injury, poisoning and procedural complications	**n (%) E**	**2 (0.8)**	**2**	**3 (1.3)**	**3**	**5 (1.1)**	**5**
Meniscus injury	n (%) E	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2
Humerus fracture	n (%) E	1 (0.4)	1	0		1 (0.2)	1
Radius fracture	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Tendon rupture	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Cardiac disorders	**n (%) E**	**0**		**4 (1.7)**	**7**	**4 (0.8)**	**7**
Acute coronary syndrome	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Acute myocardial infarction	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Atrial fibrillation	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Cardiac disorder	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Cardiac failure chronic	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Coronary artery stenosis	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Myocardial infarction	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Musculoskeletal and connective tissue disorders	**n (%) E**	**1 (0.4)**	**1**	**2 (0.9)**	**2**	**3 (0.6)**	**3**
Muscular weakness	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Osteoarthritis	n (%) E	1 (0.4)	1	0		1 (0.2)	1
Rotator cuff syndrome	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Respiratory, thoracic and mediastinal disorders	**n (%) E**	**1 (0.4)**	**1**	**1 (0.4)**	**1**	**2 (0.4)**	**2**
Chronic obstructive pulmonary disease	n (%) E	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2
Gastrointestinal disorders	**n (%) E**	**0**		**1 (0.4)**	**1**	**1 (0.2)**	**1**
Chronic gastritis	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Infections and infestations	**n (%) E**	**1 (0.4)**	**1**	**0**		**1 (0.2)**	**1**
Pneumonia	n (%) E	1 (0.4)	1	0		1 (0.2)	1
Nervous system disorders	**n (%) E**	**1 (0.4)**	**1**	**0**		**1 (0.2)**	**1**
Lumbosacral radiculopathy	n (%) E	1 (0.4)	1	0		1 (0.2)	1
Psychiatric disorders	**n (%) E**	**1 (0.4)**	**2**	**0**		**1 (0.2)**	**2**
Anxiety disorder	n (%) E	1 (0.4)	1	0		1 (0.2)	1
Panic attack	n (%) E	1 (0.4)	1	0		1 (0.2)	1

System Organ Class Preferred Term	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)		Overall Study (N = 473)	
Reproductive system and breast disorders	**n (%) E**	**0**	**1 (0.4)**	**1**	**1 (0.2)**	**1**
Endometrial disorder	n (%) E	0	1 (0.4)	1	1 (0.2)	1

Abbreviations: E = number of events; incl = including; N = number of subjects dosed with each treatment; n = number of subjects with adverse event; TEAE = treatment-emergent adverse event.

Notes: Only events observed during the Main Period are reported in this table.

%: calculated using the number of subjects dosed with each treatment (or any treatment as applicable) as the denominator (n/N*100).

All adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.

Source: Table 14.3.1.7.1

Treatment-emergent SAE in the RGB-14-P arm by PT were the following (7 patients with 9 SAEs): Thyroid cancer; meniscus injury; humerus fracture; osteoarthritis; chronic obstructive pulmonary disease; pneumonia; lumbosacral radiculopathy; anxiety disorder; and panic attack.

Treatment-emergent SAE in the Prolia arm by PT were the following (16 patients with 21 SAEs): Bladder cancer; breast cancer; clear cell renal cell carcinoma; follicular lymphoma; invasive ductal breast carcinoma; renal neoplasm; meniscus injury; radius fracture; tendon rupture; acute coronary syndrome; acute myocardial infarction; atrial fibrillation; cardiac disorder; cardiac failure chronic; coronary artery stenosis; myocardial infarction; muscular weakness; rotator cuff syndrome; chronic obstructive pulmonary disease; chronic gastritis; and endometrial disorder.

No clear pattern was identified in the SAE within or across treatment arms, also due to the overall low incidence of SAE.

3% (14/473) of participants experienced at least one SAE with the intensity of ≥Grade 3 (i.e. severe, life-threatening or death) (Prolia arm: 3.9% [9/231] versus RGB-14-P arm: 2.1% [5/242]).

None of the SAE was considered to be related to study treatment.

There was one treatment-emergent SAE (PT clear cell renal cell carcinoma) which was assessed as not being related to the IMP by the Investigator, but the Sponsor evaluated the causality as being related due to lack of alternative factors (e.g. absence of smoking history, personal or family medical history and other risk factors). The case was reported as a SUSAR to the applicable regulatory authorities.

All narratives regarding SAE are provided in the RGB-14-101 CSR.

Deaths

There was one TEAE leading to death in the Prolia arm.

Table 70: Fatal SAE by Treatment, SOC and PT – Main Period

System Organ Class Preferred Term	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)		Overall Study (N = 473)	
Any TEAEs	n (%) E	0	1 (0.4)	1	1 (0.2)	1
Cardiac disorders	**n (%) E**	**0**	**1 (0.4)**	**1**	**1 (0.2)**	**1**
Myocardial infarction	n (%) E	0	1 (0.4)	1	1 (0.2)	1

Abbreviations: E = number of events; N = number of subjects dosed with each treatment; n = number of subjects with adverse event; TEAE = treatment-emergent adverse event.

Notes: Only events observed during the Main Period are reported in this table.

%: calculated using the number of subjects dosed with each treatment (or any treatment as applicable) as the denominator (n/N*100).

All adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.

Source: Table 14.3.1.25.1

One participant with a medical history of aortic valve incompetence, bundle branch block, cardiac hypertrophy, hypercholesterolemia and hypertension received two doses of Prolia. The participant experienced a fatal SAE. An autopsy was not performed. The event was not considered by the investigator to be related to the study drug. A narrative is provided in the RGB-14-101 CSR.

2.5.8.4. Laboratory findings

Study RGB-14-001:

No clinically meaningful trends were observed in mean change from baseline values in either treatment arm with regard to haematology, coagulation, clinical chemistry, or urinalysis laboratory parameters over time.

Clinically significant laboratory abnormalities were noted for 4 participants in the RGB-14-X arm (increases in AST & ALT, CRP, cholesterol, and creatinine). All those laboratory abnormalities reported as TEAE were mild of intensity and were judged to be unrelated to study drug.

There were no clinically meaningful trends in mean change from baseline values for vital signs parameters in either treatment groups.

Study RGB-14-101:

The applicant states that there were no clinically meaningful trends in mean change from baseline values in both treatment arms in haematology or clinical chemistry laboratory parameters over time. No clinically relevant differences were observed between the two treatment groups.

Furthermore, there were no clinically meaningful trends in mean change from baseline values for vital signs parameters (diastolic blood pressure, systolic blood pressure, heart rate, respiratory rate and temperature) in both treatment arms. No clinically relevant differences were observed between the two treatment groups.

Regarding physical examination findings, overall 27 participants (19 in the RGB-14-P arms and 8 in the Prolia arm) had abnormal clinically significant physical examination results. In the RGB-14-P group, abnormal

clinically significant results were mostly observed in the musculoskeletal (7 participants) and dermatologic body systems (6 participants). In the Prolia group, abnormal clinically significant results were mostly observed in the extremities body system (4 participants).

A total of five subjects (two in the RGB-14-P arm and three in the Prolia arm) had abnormal clinically significant ECG results.

For 3 participants, ECG abnormalities were reported as TEAE:

• One participant in the RGB-14-P arm experienced a mild, non-serious TEAE of ECG abnormal on Day 183 after the first injection. The dose was interrupted for the participant and the participant recovered/resolved on Day 197. The event was not considered to be related to RGB-14-P.

• One participant in the Prolia group experienced a mild, non-serious TEAE of atrioventricular block on Day 1 after the second injection that was ongoing at the time of reporting of the CSR. The event was not considered by the investigator to be related to Prolia.

• One participant in the Prolia group had a mild, non-serious pre-treatment AE of atrioventricular block first degree on Day -3 that was ongoing at the time of reporting of the CSR.

2.5.8.5. Immunological events

RGB-14-001

No subject was ADA positive.

RGB-14-101

Table 71: Number and percentage of patients with ADA / NAb from Week 0 to Week 52 of Study RGB-14-101 – IAS

Statistic	**RGB-14-P (N = 239)**		**Prolia (N = 228)**	
	Patient n	Patient %	Patient n	Patient %
Pre-treatment (baseline)				
Patients with ADA result	239	100.0	228	100.0
ADA Positive	0	-	1	0.4
ADA Negative	239	100.0	227	99.6
Missing	0	-	0	-
NAb Positive	0	-	0	-
NAb Negative	0	-	1	0.4
Post-dose: Week 2 to Week 52				
Patients with result	239	100.0	228	100.0
ADA Positive ≥ 1 time-point up to Week 52	2	0.8	1	0.4
ADA Negative	237	99.2	227	99.6
Missing	0	-	0	-
NAb Positive ≥ 1 time-point up to Week 52	1	0.4	1	0.4
NAb Negative	1	0.4	0	0

Impact of ADA on denosumab serum concentration vs. time profiles

Neither the two RGB-14-P-treated subjects nor the single Prolia-treated subject with positive ADA signals had diminished exposure compared to ADA negative subjects.

Impact of ADA status on sCTX vs time profiles

In the 3 subjects (two in the RGB-14-P group and one in the Prolia group) in whom transient ADA positive signals were detected, there was no impact of ADA positivity on the pharmacodynamic response to RGB-14-P or Prolia as measured by the % change in sCTX vs. time from Week 0 to Week 52.

Impact of ADA status on efficacy endpoints

In the RGB-14-P treatment group, only one of the two ADA positive subjects had efficacy results available; the % change in lumbar spine BMD at Week 26 and Week 52 in this subject was higher than the mean value achieved by ADA negative subjects in the same treatment group. In the Prolia treatment group, the single ADA positive subject had a lower % change in lumbar spine BMD at Week 26 and Week 52 compared to the mean value achieved by ADA negative subjects in the same treatment group.

Overall, the paucity of ADA positive signals precluded any meaningful analysis of the relationship of ADA positive/negative status to efficacy.

Safety analysis by ADA status

The table below summarizes the proportion of subjects with (i) any treatment-emergent adverse event (TEAE), and (ii) Preferred Terms falling within MedDRA SMQ's of "hypersensitivity" or "anaphylaxis", by ADA status for each treatment group. The rationale for this analysis was to provide a broad assessment for acute and delayed reactions that might be most plausibly related to ADA, in addition to "Injection Related Reactions".

As was the case for PK, PD and efficacy parameters, the very low number of ADA positive signals renders analysis of ADA-relatedness of TEAEs as a rather meaningless exercise, particularly given the absence of any events falling within the MedDRA SMQ's of "hypersensitivity" or "anaphylaxis". Thus, these results are presented only to confirm absence of impact of the small number of detected ADA positive results on relevant safety signals.

Table 72: TEAE's with Preferred Terms falling within MedDRA SMQs of hypersensitivity or anaphylaxis by ADA status and treatment from Week 0 to Week 52 – IAS

	RGB-14-P (N=239)						Prolia (N=227)					
	ADA Positive (N=2)			ADA Negative (N=237)			ADA Positive (N=1)			ADA Negative (N=227)		
Category	n	%	Ev.v	n	%	Ev.v	n	%	Ev.v	n	%	Ev.v
Any TEAE - Overall	1	50.0	2	157	66.2	513	1	100	5	150	66.1	432
Any TEAE of special interest	0			15	6.3	16	0			12	5.3	13
SMQ = hypersensitivity	0			13	5.5	14	0			9	4.0	10
Conjunctivitis	0			2	0.8	2	0			2	0.9	2
Dermatitis allergic	0			3	1.3	3	0			1	0.4	1
Pruritus	0			3	1.3	3	0			0		
Rhinitis allergic	0			1	0.4	1	0			2	0.9	2
Eczema	0			2	0.8	2	0			0		
Conjunctivitis allergic	0			1	0.4	1	0			0		
Injection site rash	0			0			0			1	0.4	1
Periorbital swelling	0			0			0			1	0.4	1
Rash	0			1	0.4	1	0			0		
Rash erythematous	0			1	0.4	1	0			0		
Rash pruritic	0			0			0			1	0.4	1
Swelling of eyelid	0			0			0			1	0.4	1
Urticaria	0			0			0			1	0.4	1
SMQ = anaphylaxis	0			7	3.0	7	0			7	3.1	7
Cough	0			1	0.4	1	0			3	1.3	3
Pruritus	0			3	1.3	3	0			0		
Periorbital swelling	0			0			0			1	0.4	1
Rash	0			1	0.4	1	0			0		
Rash erythematous	0			1	0.4	1	0			0		
Rash pruritic	0			0			0			1	0.4	1
Renal failure	0			1	0.4	1	0			0		
Swelling of eyelid	0			0			0			1	0.4	1
Urticaria	0			0			0			1	0.4	1

MedDRA version 26.0
N = total number of subjects in the corresponding treatment group and analysis set
n =|number of subjects with at least one TEAE falling within the corresponding category
Ev.n = number of events in the corresponding category and treatment group
Source: Figure 2.5.1 in ISI Tables for Study RGB-14-101

2.5.8.6. Discontinuation due to adverse events

Study RGB-14-001:

None of the study participants discontinued prematurely due to adverse events.

Study RGB-14-101:

Discontinuation from study treatment

Overall, 4 participants experienced a TEAE leading to IMP discontinuation during the Main Period. The percentage of participants experiencing at least one TEAE leading to treatment discontinuation was similar in the two treatment arms (RGB-14-P arm: 0.8% [2/242]; Prolia arm: 0.9% [2/231]).

TEAE that led to IMP discontinuation were thyroid cancer and osteitis reported in the RGB-14-P arm (1 [0.4%] participant each), as well as breast cancer and follicular lymphoma in the Prolia arm (1 [0.4%] participant each). Of these, only the event of osteitis was considered related to the IMP.

Table 73: TEAE leading to Discontinuation of IMP by Treatment, SOC and PT– Main Period

System Organ Class Preferred Term	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Any TEAEs	n (%) E	2 (0.8) 2	2 (0.9) 2	4 (0.8) 4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	n (%) E	1 (0.4) 1	2 (0.9) 2	3 (0.6) 3
Breast cancer	n (%) E	0	1 (0.4) 1	1 (0.2) 1
Follicular lymphoma	n (%) E	0	1 (0.4) 1	1 (0.2) 1
Thyroid cancer	n (%) E	1 (0.4) 1	0	1 (0.2) 1
Musculoskeletal and connective tissue disorders	n (%) E	1 (0.4) 1	0	1 (0.2) 1
Osteitis	n (%) E	1 (0.4) 1	0	1 (0.2) 1

Abbreviations: E = number of events; IMP = investigational medicinal product; incl = including; N = number of subjects dosed with each treatment; n = number of subjects with adverse event; TEAE = treatment-emergent adverse event.

Notes: Only events observed during the Main Period are reported in this table.

%: calculated using the number of subjects dosed with each treatment (or any treatment as applicable) as the denominator (n/N*100).

IMP is RGB-14-101 or Prolia.

All adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.

Source: Table 14.3.1.13.1.1

Discontinuation from overall study

Overall, 5 participants (1.1%) experienced at least one TEAE leading to participant discontinuation during the Main Period. Participant discontinuation implied discontinuation from the study. The percentage of participants experiencing at least one TEAE leading to participant discontinuation was similar in the two treatment arms (RGB-14-P arm: 0.8% [2/242]; Prolia arm: 1.3% [3/231]).

TEAE that led to participant discontinuation were thyroid cancer and osteitis reported in the RGB-14-P arm (1 [0.4%] participant each), as well as breast cancer, follicular lymphoma and a fatal event in the Prolia arm (1 [0.4%] participant each). Of these, only the event of osteitis was considered related to the IMP.

Table 74: TEAE leading to Subject Discontinuation from the Study by Treatment, SOC and PT – Main Period

System Organ Class Preferred Term	Statistic	RGB-14-P (N = 242)		Prolia (N = 231)		Overall Study (N = 473)	
Any TEAEs	n (%) E	2 (0.8)	2	3 (1.3)	3	5 (1.1)	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**n (%) E**	**1 (0.4)**	**1**	**2 (0.9)**	**2**	**3 (0.6)**	**3**
Breast cancer	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Follicular lymphoma	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Thyroid cancer	n (%) E	1 (0.4)	1	0		1 (0.2)	1
Cardiac disorders	**n (%) E**	**0**		**1 (0.4)**	**1**	**1 (0.2)**	**1**
Myocardial infarction	n (%) E	0		1 (0.4)	1	1 (0.2)	1
Musculoskeletal and connective tissue disorders	**n (%) E**	**1 (0.4)**	**1**	**0**		**1 (0.2)**	**1**
Osteitis	n (%) E	1 (0.4)	1	0		1 (0.2)	1

Abbreviations: E = number of events; incl = including; N = number of subjects dosed with each treatment; n = number of subjects with adverse event; TEAE = treatment-emergent adverse event.

Notes: Only events observed during the Main Period are reported in this table.

%: calculated using the number of subjects dosed with each treatment (or any treatment as applicable) as the denominator (n/N*100).

All adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.

Source: Table 14.3.1.13.1

2.5.8.7. Post marketing experience

Not applicable.

2.5.9. Discussion on clinical safety

Safety data collection/ exposure

The comparative safety of RGB-14-P/ RGB-14-X and Prolia/ Xgeva has been evaluated in two clinical studies, a Phase I PK study in healthy male subjects (RGB-14-001) and a Phase III efficacy and safety study in female

patients with postmenopausal osteoporosis (RGB-14-101). In both studies the therapeutic dose of 60 mg was investigated.

Safety and tolerability were investigated in the safety analysis set (SAF), respectively. In study RGB-14-101, the SAF comprised 473 women, and in study RGB-14-001, the SAF comprised 165 healthy male volunteers. No pooling of safety data was performed as study -001 was conducted in healthy male subjects and study -101 in female subjects with PMO. Safety focus in both studies were AEs, TEAEs, and SAEs. No adverse events of special interest (AESIs) were predefined.

The safety assessments performed during studies -001 and -101 are considered appropriate, including the number and frequency of safety assessments in the main and transition period in study -101.

In study -001, all randomised subjects received a single dose of the test products. In study -101, all randomised patients received the first injection, and a similar number of patients (approximately 94%) in the two study arms received the second injection. The number of patients receiving a third injection at the beginning of the transition period is not reported at this point.

Study RGB-14-001 has been completed; for study RGB-14-101, the Main Period has been completed, whereas the Transition Period was still ongoing at DCO for the initial submission. Therefore, safety data from the Transition Period of study RGB-14-101 were submitted during the procedure.

The size of the safety database and duration of collection of safety data are considered adequate for the purpose of similarity assessment.

The previous medical history seems reasonably balanced between groups.

Baseline disease-specific characteristics such as BMD, T-score, P1nP and sCTX values were balanced between the treatment arms.

Results

Adverse events

In study RGB-14-001, overall 128 (77.6%) subjects experienced a total of 424 TEAE. The proportion of subjects who experienced at least 1 TEAE was similar between RGB-14-X and US-Xgeva (74.7% (n=62) with 211 events for RGB-14-X versus 80.5% (n=66) with 213 events for US-Xgeva).

Also on SOC level, comparable incidences were observed between the RGB-14-X arm and the US-Xgeva arm.

The most frequently reported TEAE on PT level were nasopharyngitis (RGB-14-X: 21.7% versus Xgeva: 22.0%), COVID-19 (RGB-14-X: 20.5% versus Xgeva: 19.5%), and headache (RGB-14-X: 14.5% versus Xgeva: 15.9%). TEAE were overall well balanced between the treatment groups.

Most participants reported TEAE that were mild or moderate in intensity. Three (1.8%) participants reported 4 TEAE that were severe in intensity (i.e. Grade 3 or higher). These events were considered not related to the study drug. A tabulated summary of frequencies of TEAE by SOC/PT and by grade (mild/moderate versus severe) for both treatment arms has been provided during the procedure, as requested.

There were no TEAE leading to withdrawal of participants from study or death.

Treatment-related AE were reported with the similar frequency in both treatment arms (RGB 14 X: 30.1% - 25 subjects; Xgeva: 30.5% -30 subjects). All reported ADRs were mild or moderate in severity, none was severe. Any observed differences between treatment arms in mild/moderate ADRs are not considered to be of clinical relevance, especially due to low number of subjects with ADRs in each arm.

Incidences of TEAE considered related to study drug reported in at least 3% participants in any treatment arm were overall low: Dizziness postural was reported by 6.0% of participants in the RGB-14-X arm versus 4.9% in the Xgeva arm. Headache was reported by 4.8% of participants in the RGB-14-X arm versus 3.7% in the Xgeva arm. Fatigue was reported by 3.6% participants in the RGB-14-X arm versus 2.4% participants in the Xgeva arm. Back pain was reported by 3.6% participants in the RGB-14-X arm versus 0% participants in the Xgeva arm. These events were mild in intensity with an onset on Day 1 or Day 2 and resolved within 1-4 days of onset.

There were slight numerical imbalances seen on SOC and PT level between the RGB-14-X and US-Xgeva arms, but these are not considered clinically meaningful.

Injection site reactions were reported by 4 participants (2 in each treatment group). These events were considered to be related to the IMP. None of the injection site reactions were severe or worse (i.e. ≥Grade 3) in severity.

Overall, the safety findings of study -001 gave no cause for concern.

In study RGB-14-101, a total of 953 TEAE were reported in 310 subjects (65.5%) during the Main Period: 158 subjects (65.3%; 515 events) in the RGB-14-P arm and 152 subjects (65.8%; 438 events) in the Prolia arm with the proportion of patients experiencing any TEAE, as well as the total number of TEAE between the treatment groups being comparable. The safety findings from study RGB-14-101 were overall in line with the known safety profile of Prolia.

Overall, the most frequently reported AEs by PT were COVID-19 (RGB-14-P: 9.9% versus Prolia: 10.4%, respectively), nasopharyngitis (9.5% versus 8.7%), upper respiratory tract infection (9.5% versus 4.3%), and hypocalcaemia (9.1% versus 9.5%).

Except for the PT upper respiratory tract infection, which was reported at a higher incidence in the RGB-14-P arm than in the Prolia arm (9.5% vs 4.3%), the incidences of the other most frequently reported PTs were similar in the two treatment groups. None of the upper respiratory tract infections were reported as SAE. Upper respiratory tract infection AEs considered treatment-related were reported in 4 subjects (1.7%) in the RGB-14-P arm, which corresponds to the frequency of Upper respiratory tract infection ADR detailed in the Prolia EU Product Information (common frequency [≥ 1/100 to < 1/10]). In the Prolia arm, 1 (0.4%) subject experienced an Upper respiratory tract infection AE considered related. The analyses provided do not give cause for concern, since the observed differences regarding upper respiratory tract infections TEAE disappeared after including the evaluation of "relatedness". No imbalance of clinical relevance was detected between the treatment arms. This is substantiated by the comparison of infectious AEs associated with the upper respiratory system by treatment arm, SOC and PT, showing no clinically meaningful differences between the treatment arms.

Overall, 10.1% (48/473) of participants had at least one TEAE of COVID-19 infection. The percentage of participants was comparable between the RGB-14-P and Prolia arms. The COVID-19 infections reported in most participants in both treatment groups were mild in severity. None of the COVID-19 infections reported were severe or serious. Except for 1 (0.4%) participant in the Prolia arm, none of the other participants experienced COVID-19 infections that were considered related to the study drug. None of the COVID-19 infections led to participant discontinuation from treatment or the study.

Frequencies and pattern of TEAE observed in study RGB-14-101 gave no cause for concern.

Overall, 119 TEAE in 68 participants (14.4%) were considered related to study treatment by the investigator during the Main Period. The number of participants experiencing at least one TEAE that was considered to be

related was comparable between the two treatment arms (RGB-14-P arm: n=36 [14.9%]; Prolia arm: n=32 [13.9%]).

Hypocalcaemia, a known ADR of denosumab, was the most frequently reported TEAE that was considered related to the IMP; it was reported by a similar number of participants in the RGB-14-P and Prolia groups (n=16 in each arm; 6.6% and 6.9%, respectively).

Injections site reactions were reported from 2 subjects in the US-Prolia arm with 1 TEAE for each subject, respectively. The intensity of the TEAE was rated as mild. Both TEAEs were considered related to study treatment.

AESI

For study RGB-14-101, no AESI have been defined by the applicant in the study protocol. Only fracture TEAE have been presented as "significant TEAE" for their denosumab biosimilar RGB-14-P. With the responses to the d120 LoQ, the applicant provides an appropriate list of AESI for their biosimilar product, reflecting the known risks for the originator Prolia, which are: hypocalcaemia, skin infection leading to hospitalisation, osteonecrosis of the jaw, hypersensitivity reactions, atypical femoral fracture, and hypercalcaemia in paediatric patients. Furthermore, safety analyses have been provided for those AESI defined. Those analyses do not give any cause for concern, since no clinically meaningful differences were observed between the study arms.

Fracture TEAE assessment was a secondary safety endpoint in the study protocol of study RGB-14-101 and was therefore presented as "other significant TEAE". Overall, 5.7% (27/473) of participants experienced 32 fracture TEAE during the Main Period. Fracture TEAE were more frequently reported in the Prolia arm (7.8% [18/231] with 20 events) than in the RGB-14-P arm (3.7% [9/242] with 12 events). Overall 3 participants experienced at least one fracture TEAE that was Grade 3 or worse in severity (2 participants in the RGB-14-P arm experiencing foot fracture and humerus fracture, respectively, and 1 participant in the Prolia arm experiencing a radius fracture).

None of the fracture TEAE reported during the Main Period were considered to be related to the IMP.

Two participants experienced 2 fracture SAE during the Main Period (1 participant in each treatment arm had 1 event). The fracture SAE reported in the RGB-14-P was humerus fracture by PT; in the Prolia group it was radius fracture. Both fracture SAE reported were severe; however, they were not considered related to study treatment.

During the Transition period, no differences were detected among the three treatment arms regarding the subjects who experienced fracture AEs, also taking into consideration the overall low incidence of fracture AEs. No severe fracture AE was reported in either treatment arm.

Serious AE/ deaths

In study RGB-14-001, 2 SAEs were reported in two participants (1 event of nerve compression in the US-Xgeva arm and 1 event of influenza in the RGB-14-X arm) and were considered not related to the study drug. Both SAEs resolved, and the participants completed the study. No concerns arise from the assessment of SAE in this study.

No deaths were reported in the study.

In study RGB-14-101, overall, 23 participants (4.9%) experienced 30 treatment-emergent SAE during the 52-Week Main Period. A higher number of participants in the US-Prolia arm than in the RGB-14-P arm

experienced at least one SAE (16 subjects with 21 events [6.9%] vs 7 subjects with 9 events [2.9%], respectively).

SAEs were most frequently reported in the SOCs of Neoplasms benign, malignant and unspecified (7 subjects [1.5%]), Injury, poisoning and procedural complications (5 subjects [1.1%]) followed by Cardiac disorders (4 subjects [0.8%]).

Treatment-emergent SAE in the RGB-14-P arm by PT were the following (7 patients with 9 SAE): Thyroid cancer; meniscus injury; humerus fracture; osteoarthritis; chronic obstructive pulmonary disease; pneumonia; lumbosacral radiculopathy; anxiety disorder; and panic attack.

Treatment-emergent SAE in the Prolia arm by PT were the following (16 patients with 21 SAE): Bladder cancer; breast cancer; clear cell renal cell carcinoma; follicular lymphoma; invasive ductal breast carcinoma; renal neoplasm; meniscus injury; radius fracture; tendon rupture; acute coronary syndrome; acute myocardial infarction; atrial fibrillation; cardiac disorder; cardiac failure chronic; coronary artery stenosis; myocardial infarction; muscular weakness; rotator cuff syndrome; chronic obstructive pulmonary disease; chronic gastritis; and endometrial disorder.

No clear pattern was identified in the SAE within or across treatment arms, also due to the overall low incidence of SAE.

3% (14/473) of participants experienced at least one SAE with the intensity of ≥ Grade 3 (i.e. severe, life-threatening or death) (Prolia arm: 3.9% versus RGB-14-P arm: 2.1%).

None of the reported SAE was considered to be related to study treatment.

There was one treatment-emergent SAE (PT clear cell renal cell carcinoma) which was assessed as not being related to the IMP by the investigator, but the sponsor evaluated the causality as being related due to lack of alternative factors (e.g. absence of smoking history, personal or family medical history and other risk factors). The case was reported as a SUSAR to the applicable regulatory authorities.

Overall, reported SAE in postmenopausal women with osteoporosis at high risk of fracture do not give rise of concern regarding the proposed similarity between RGB-14-P and US-Prolia. Reported SOCs and PTs appear balanced between treatment groups (i.e. imbalances do not exceed a difference of 2 subjects more/less). No specific pattern could be identified regarding SAE within or across the study arms.

There was one TEAE leading to death reported in the Prolia arm. The event was considered unrelated to study treatment.

Overall, no concern arises regarding the proposed similarity of RGB-14-P and (US-)Prolia from the reported SAE and deaths.

Discontinuation due to adverse events

None of the study participants in study RGB-14-001 discontinued prematurely due to adverse events.

In study RGB-14-101, overall 4 subjects experienced 4 TEAE leading to discontinuation of study treatment during the Main Period. The TEAEs that led to IMP discontinuation were: thyroid cancer and osteitis reported in the RGB-14-P arm (1 participant each), as well as breast cancer and follicular lymphoma in the Prolia arm (1 participant each). Of these, only the event of osteitis was considered related to the IMP. All events leading to discontinuation of study IMP were classified as SAE, except for the event of osteitis.

With regard to discontinuation from overall study participation 5 subjects discontinued due to TEAE (i.e. the 4 subjects who discontinued study treatment, plus the subject who died).

Overall, no concerns arise from TEAE leading to discontinuation of study drug for the expected safety of RGB-14-P.

Laboratory and other findings

No clinically significant imbalances have been identified between the treatment arms with regard to haematology values, clinical chemistry parameters, vital signs, physical examination findings and ECG results as well as AEs reported in association with these results during either of the treatment periods.

Immunogenicity

After single dosing in Study RGB-14-001, no subject was tested ADA positive during the study.

In Study RGB-14-101 in patients with PMO, one subject in the Prolia group was positive for ADA at baseline. Upon dosing, only three subjects (2 subjects in RGB-14-P, one subject in the Prolia group) were found to be treatment induced transient ADA positive until week 52. Two subjects (one each per group) were NAb positive as well. Overall, the observed low immunogenicity with both treatments is in line with the low historical rate of ADAs for Prolia (<1%). There was no impact of ADAs on PK, PD, efficacy and safety until week 78 observed.

2.5.10. Conclusions on the clinical safety

Based on the provided data of two clinical studies, one in healthy male volunteers and one in female PMO patients, no unexpected safety concerns were detected. The observed safety findings correspond to the known safety profile of the reference products Prolia and Xgeva and were overall balanced between treatment arms.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Osteonecrosis of the jaw Atypical femoral fracture Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons
Important potential risks	Cardiovascular events Malignancy Delay in diagnosis of primary malignancy in giant cell tumour of bone Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons
Missing information	Patients with prior intravenous bisphosphonate treatment Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Osteonecrosis of the jaw	Routine risk minimisation measures *SmPC section 4.4, where guidance on oral hygiene and dental management is provided* *SmPC sections 4.3, 4.8 and 5.1* *PL sections 2 and 4*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up questionnaire for osteonecrosis of the jaw* Additional pharmacovigilance activities *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status: *restricted medical prescription* Additional risk minimisation measures *Patient card*	
Atypical femoral fracture	Routine risk minimisation measures *SmPC section 4.4, where recommendation for reporting potential symptoms is provided* *SmPC section 4.8* *PL sections 2 and 4* Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *AE follow-up questionnaire for osteonecrosis of the jaw* Additional pharmacovigilance activities *None*
Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	Routine risk minimisation measures *SmPC section 4.4, where recommendation regarding monitoring of calcium levels periodically after treatment discontinuation is provided* *SmPC section 4.8* *PL sections 2 and 4* Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*

Important potential risks		
Cardiovascular events	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*
Malignancy	Routine risk minimisation measures *SmPC section 4.4, where recommendation regarding monitoring of radiological signs of malignancy, new*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	radiolucency or osteolysis is provided *SmPC sections 4.8 and 5.1* *PL section 4* Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	
Delay in diagnosis of primary malignancy in giant cell tumour of bone	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*
Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	radiolucency or osteolysis is provided *SmPC sections 4.8 and 5.1* *PL section 4* Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	
Delay in diagnosis of primary malignancy in giant cell tumour of bone	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*
Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*

Missing information		
Patients with prior intravenous bisphosphonate treatment	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	Routine risk minimisation measures Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities *None*
Off-label use in patients with giant cell tumour	Routine risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
of bone that is resectable where resection is unlikely to result in severe morbidity	Legal status: *restricted medical prescription* Additional risk minimisation measures *None*	*None* Additional pharmacovigilance activities *None*

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.2 is acceptable.

2.7. Pharmacovigilance

2.7.1. 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.

2.7.2. Periodic Safety Update Reports submission requirements

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

2.8. Product information

2.8.1. User consultation

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

2.8.2. Quick Response (QR) code

A request to include a QR code in the Package Leaflet has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code: Statutory information as well as a video for instruction for use.

2.8.3. Additional monitoring

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

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

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

RGB-14-P and RGB-14-X were developed as biosimilar products to the reference products Prolia and Xgeva (INN: denosumab), respectively. The active pharmaceutical ingredient in RGB-14-P and RGB-14-X is denosumab. The project code for the proposed biosimilar denosumab drug substance (DS) is RGB-14, while the project codes for the proposed biosimilar drug products (DP) of Prolia and Xgeva are RGB-14-P and RGB-14-X, respectively.

This MAA under the Centralized Procedure is an application for the proposed biosimilar Yaxwer to Xgeva according to Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The application has been submitted in accordance with Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for

a biosimilar medicinal product. Prolia and Xgeva were originally approved in the European Union on 13/07/2011 (marketing authorisation holder: Amgen Europe B.V.).

Denosumab, is a human monoclonal antibody of the IgG2 subtype that inhibits the interaction of receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL) with RANK on the surface of osteoclasts. This inhibition prevents the development (genesis, maturation, activation and survival) of osteoclasts, the cells responsible for bone resorption that play a critical role in bone modelling and remodelling during growth. The prevention of this RANKL/RANK interaction is the main mechanism of action of denosumab across all its approved indications.

The reference product Xgeva received approval for two presentations (Xgeva 70 mg/1.7 mL solution (120 mg) for injection in a vial and Xgeva 120 mg/1 mL solution (120 mg) in a pre-filled syringe for s.c. use.

The applicant proposes one presentation of the biosimilar RGB-14-X under the name Yaxwer: 70 mg/1.7 mL solution (120 mg) for injection in a vial for s.c. use.

The proposed indications are the same as approved for the reference product Xgeva that is indicated for:

- Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone.
- Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

For this MAA, the applicant has claimed all of the indications of the reference product Xgeva.

Quality aspects

A comprehensive analytical biosimilarity exercise comparing RGB-14-X with the reference medicinal products EU-Xgeva has been performed. A large number of batches, which can be expected to sufficiently reflect product variability of both the proposed biosimilar and the reference product, was analysed. The RGB-14-X batches have been manufactured according to the clinical and intended commercial process. A risk assessment identified a comprehensive QA list tested during the study. A suitable statistical approach was used for quality (biosimilarity) range definition, where appropriate. The approach is in general considered acceptable taking the high number of reference product batches into account. High similarity was concluded, given that 90% of data are fall into the quality range. Similarity was concluded, given that 50% of data are fall into the quality range. In this regard, the applicant provided sufficient scientific justifications.

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.

The in-depth analyses with sensitive methods showed some minor differences between both molecules. However, the differences are mainly due to high assays variability or the values are overall very low. Scientific justifications have been provided to show that the differences are not clinically meaningful.

In addition, an extensive comparative forced degradation study complements the biosimilarity assessment. These complementary studies are adequately designed to support the conclusion drawn.

Clinical aspects

The clinical development program for Yaxwer included one completed Phase I study in healthy male subjects (study RGB-14-001) and one ongoing Phase III study in female patients with postmenopausal osteoporosis (RGB-14-101).

Study RGB-14-001 was a randomised, double-blind, 2-arm, single-dose, parallel comparative pharmacokinetic and pharmacodynamic Phase I study comparing RGB-14-X versus US-Xgeva in healthy male subjects.

A total of 165 healthy male subjects (RGB-14-X n=83, US-Xgeva n=82) were enrolled and randomised in a 1:1 ratio to receive a single dose of 60 mg of either RGB-14-X or US-Xgeva via s.c. injection. Subjects were treated on Day 1 and followed up for 252 days for PK, PD, safety and immunogenicity assessments.

The primary objective was to establish PK equivalence between RGB-14-X and US-Xgeva using the co-primary endpoints of AUC0-inf and Cmax. Bioequivalence was concluded if the ratio of GLSM and corresponding 90% CI are contained within the predefined bioequivalence range of 0.80 to 1.25. Secondary objectives included additional PK parameters, PD assessments, safety and immunogenicity.

Study RGB-14-101 was a randomised, double-blind, parallel, multicentre, 2-arm Phase III study to compare the efficacy, safety and immunogenicity of RGB-14-P vs. US-Prolia in postmenopausal women with osteoporosis.

Patients received either RGB-14-P or US-Prolia at a dose of 60 mg every 6 months, which is the approved dose and regimen. The study consisted of a Main Period (52 weeks) with 2 denosumab doses administered, and of a Transition period (26 weeks) with a third denosumab dose administered.

The study was conducted in Poland, Bulgaria, Hungary, Czech Republic, Spain, Italy, the Ukraine and the USA.

A total of 473 patients were randomised 1:1 to receive either RGB-14-P or US-Prolia in the Main Period. Randomisation schedule was stratified by previous use of bisphosphonates (yes/no) and geographical region (Europe, US).

The Transition Period was applicable to a subset of patients (n=198): 132 participants who received Prolia during the Main Period were to be re-randomised (1:1) to receive either a third dose of RGB-14-P or US-Prolia in a double-blinded manner; another 66 participants who received RGB-14-P during the Main Period would continue to receive a third dose of RGB-14-P.

A total of 473 patients received one dose, and 446 patients received two doses of study treatment.

For the demonstration of efficacy, the difference in LS mean %CfB in lumbar spine BMD at Week 52 was assessed by DXA. The co-primary PD endpoint was the AUEC of percent change from baseline in sCTX (0-m6) concentration until week 26 (AUEC of %CfB in sCTX(0-m6). Bioequivalence was established if the the ratio of GLSM and corresponding 95% CI are contained within the predefined bioequivalence range of 0.80 to 1.25. Secondary endpoints included additional efficacy and PD parameters.

The safety profiles of RGB-14-P, RGB-14-X and the respective reference products were assessed in the Phase I study as well as in the Phase III study.

3.2. Results supporting biosimilarity

Quality

For most quality attributes including multiple attributes covering the mechanism of action and other functional activities, RGB-14-X was demonstrated to be highly similar to the reference product EU-Xgeva. The observed minor analytical differences have been adequately justified regarding their impact on clinical performance of the product. Further evidence for biosimilarity is provided by the results of a comparative forced degradation study and extended characterisation of charge variants.

Clinical aspects

PK

In study RGB-14-001, PK assessments demonstrated that the geometric means of the co-primary endpoints C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}last}$ were comparable between treatment arms and the primary statistical analysis demonstrated that the 90% CIs of GLSM ratios were well contained within the acceptable bioequivalence range (0.80 – 1.25). Overall, bioequivalence acceptance criteria for the co-primary endpoints were met. Additional PK parameters (t_{max}, terminal $t_{1/2}$, and partial AUCs) also supported the biosimilarity assessment.

In study RGB-14-101, there were no pre-specified PK endpoints. Mean serum concentrations up to Week 78 were overall comparable between the RGB-14-P and Prolia group, even after switching from Prolia to RGB-14-P.

PD

In study RGB-14-001, secondary PD endpoints included the percentage change from baseline (%CfB), the area under the effect curve (AUEC) of %CfB in sCTx, and the maximum effect (I_{max}) of sCTx. Descriptive analyses of the mean sCTx (concentration and %CfB) over time showed no significant differences between RGB-14-X and US-Xgeva. Geometric mean AUEC of %CfB in sCTx and I_{max} of sCTx were comparable between the treatment groups.

In study RGB-14-101, the co-primary PD endpoint of this study was met: The ratio of the geometric means of the AUEC of %CfB in sCTX concentration for the Main Period between the RGB-14-P and Prolia treatment group was 1.01 with the 95% CIs fully contained within acceptable bioequivalence range (0.978, 1.046). Results of the secondary PD parameters up to Week 78 also support biosimilarity.

Efficacy

In study RGB-14-101, the primary efficacy analysis resulted in an estimated difference in %CfB in lumbar spine BMD after 52 weeks between the RGB-14-P and the US-Prolia group of 0.34 (95% CI = -0.402, 1.090). Thus, the 95% CI was contained within the predefined equivalence margin of [-1.45, 1.45], supporting the claim of biosimilarity.

The secondary efficacy analysis of %CfB BMD of vertebral (Lumbar spine) and non-vertebral (Total Hip and Femoral Neck) structures did not reveal clinically remarkable difference between RGB-14-P and RP and showed similar improvement in BMD of all vertebral and non-vertebral structures over time (Main Period, Week 26 to Week 52 and Transition Period, up to Week 78) being supportive for the primary endpoint outcome.

Safety

In the Phase I study RGB-14-001, the safety profile in healthy men was comparable between RGB-14-X and US-Xgeva. Frequencies and pattern of TEAE gave no cause for concern.

Two SAEs were reported from 2 participants in the study (1 in each treatment arm); they were judged unrelated to study treatment. No deaths occurred in the study, and there were no discontinuations from study treatment or from the entire study reported due to adverse events.

In the Phase III study RGB-14-101, the proportion of female PMO patients experiencing any TEAE as well as the total number of TEAE were comparable between the treatment arms. The safety findings were overall in line with the know safety profile of Prolia - frequencies and pattern of TEAE observed in study RGB-14-101 gave no cause for concern. The number of participants experiencing related TEAE that was considered to be related was comparable between the two treatment arms. Hypocalcaemia, a known adverse reaction for Prolia, was the most frequently reported TEAE that was considered related to the IMP; it was reported by a similar number of participants in the RGB-14-P and Prolia groups (n=16 in each arm).

With regard to SAE, a higher number of participants in the US-Prolia arm than in the RGB-14-P arm experienced at least one SAE (16 subjects with 21 events [6.9%] vs 7 subjects with 9 events [2.9%], respectively). None of the reported SAE was considered to be related to study treatment. There was one TEAE leading to death reported in the Prolia arm, which was considered unrelated to study treatment. Overall, no concern arises regarding the proposed similarity of RGB-14-P and (US-)Prolia from the reported SAE and deaths.

Similar numbers of patients in both treatment arms discontinued from study treatment due to adverse events (n=2 per treatment arm).

Based on the provided safety data of two clinical studies, no unexpected safety concerns were detected. The observed safety findings correspond to the known safety profile of the reference products Prolia and Xgeva and were overall balanced between treatment arms.

Immunogenicity

After single dosing in study RGB-14-001, no subject was tested ADA positive during the study.

In study RGB-14-101 in patients with PMO, one subject in the Prolia group was positive for ADA at baseline. Upon dosing, only three subjects (2 subjects in RGB-14-P, one subject in the Prolia group) were found to be treatment induced transient ADA positive until week 52. Two subjects (one each per group) were NAb positive as well. During the Transition Period, only one subject in the Prolia-Prolia group was transiently ADA and NAb positive at week 54 and 56. Overall, the observed low immunogenicity with both treatments is in line with the low historical rate of ADAs for Prolia (<1%). There was no impact of ADAs on PK, PD, efficacy and safety until week 78 observed.

3.3. Uncertainties and limitations about biosimilarity

Quality

None

Clinical aspects

PK

None

PD

None

Efficacy

None

Safety

None

Immunogenicity

None

3.4. Discussion on biosimilarity

Quality

In summary, the analytical comparability exercise is adequately designed as described above. The results show only minor differences between RGB-14-X and EU-Xgeva. These minor differences observed are not expected to impact clinical performance of RGB-14-X. From a quality perspective there are no uncertainties regarding the biosimilarity claim of RGB-14-X to EU-Xgeva.

Clinical aspects

PK and PD

In summary, the provided PK and PD data support biosimilarity of RGB-14-X with US-Xgeva and RGB-14-P and US-Prolia.

Efficacy

In summary, the provided efficacy data support the biosimilarity between RGB-14-P and US-Prolia.

Safety

A sufficiently large number of patients was treated with either RGB-14-X/ RGB-14-P or the originator products, Prolia/ Xgeva, in the two clinical studies. The overall study duration of 52 weeks in the Main Period of the Phase 3 study is also considered adequate for the purpose of similarity assessment.

Overall, the submitted safety and immunogenicity data are considered supportive for demonstration of biosimilarity. There were no clinically relevant differences in the safety profiles of RGB-14 and the reference product Prolia/ Xgeva identified. In general, the frequencies and nature of the adverse events were comparable between the biosimilar and the RMP.

The complete final CSR with the full safety and immunogenicity data set for study -101 has been submitted by the applicant during the procedure and is considered supportive for further substantiation of similarity between the biosimilar candidate and Prolia/ Xgeva.

Immunogenicity

Overall, immunogenicity data do not indicate any impact of ADAs/Nabs on the PK, PD, efficacy and safety of RGB-14-X and RGB-14-P.

3.5. Extrapolation of safety and efficacy

RGB-14-P and RGB-14-X were developed as biosimilar products to the reference products Prolia and Xgeva. The active substance of RGB-14-P, RGB-14-X and both originators, denosumab, is a human monoclonal antibody of the IgG2 subtype that inhibits the interaction of receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL) with RANK on the surface of osteoclasts. This inhibition prevents the development (genesis, maturation, activation and survival) of osteoclasts, the cells responsible for bone resorption that play a critical role in bone modelling and remodelling during growth. 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.

As presented in the Guideline of Bioequivalence and EMA scientific advice 2019, extrapolation of clinical efficacy and safety data to other indications of the originator product not studied within this clinical package is possible, if similarity is shown on quality and extended functional characterisation, and in clinical phase I and phase III studies.

The extrapolation is further supported by the fact that the known PK, PD, safety and immunogenicity profile of denosumab as summarised in the product information for Prolia/Xgeva is comparable across the approved indications and patient populations.

Furthermore, the clinical data were derived from healthy volunteers and post-menopausal women with osteoporosis. These are regarded sensitive populations in terms of evaluating biosimilarity of RGB-14 and the reference product.

Of note, this only applies to indications for which Yaxwer is approved in the EU, thus NOT Treatment of hypercalcaemia of malignancy refractory to bisphosphonate therapy (i.e. additional indication in the US and Australia).

Based on the above, the safety and efficacy profile of Yaxwer as assessed in the PMO indication can be extrapolated to all indications applied for Yaxwer.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Yaxwer is considered biosimilar to Xgeva. 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 Yaxwer is favourable in the following indication(s):

> Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone
>
> Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity

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 restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

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 card regarding osteonecrosis of the jaw is implemented.