Protocol 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

Protocol number: RGB-14-101

ClinicalTrails.gov Identifier: NCT05087030

Date of protocol: 28-March-2023

Title Page

Protocol 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
Short Title:	Comparative Efficacy and Safety Study of RGB-14-P and Prolia® in Women with Postmenopausal Osteoporosis
Compound:	RGB-14-P (test product) and Prolia® (reference product)
Indication:	Postmenopausal Osteoporosis
Study Sponsor:	Gedeon Richter Plc. 1103 Budapest, Gyömrői út 19-21 Hungary
Protocol Number:	RGB-14-101
Study Phase:	Phase III
Regulatory Agency Identifying Number:	IND 146025
European Clinical Trials Database (EudraCT) Number:	2020-006017-38
Approval Date:	Final Version 5.0 28Mar2023

This clinical study will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Tripartite Guideline for Good Clinical Practice (GCP) E6(R2), the protocol and its amendments, the Declaration of Helsinki and with other applicable regulatory requirements.

Confidentiality Statement

Sponsor Signatory:

PPD

PPD

Medical Monitor Name and Contact Information will be provided in the Investigator Site File.

Key Study Team contact details will be provided in the Investigator Site File.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Version**	**Date**
Non-Substantial Amendment 2; Global Amendment	Final 5.0	28 Mar 2023
Substantial Amendment 3; Global Amendment	Final 4.0	19 Jan 2023
Substantial Amendment 2; Global Amendment	Final 3.0	10 Jan 2022
Substantial Amendment 1; Country Specific – United States	Final 2.0	03 Aug 2021
Non-Substantial Amendment 1; Country Specific - Czech Republic	Final 1.1	20 July 2021
Original Protocol	Final 1.0	10 March2021

Non-Substantial Amendment 2 (28 Mar 2023)

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

Overall Rationale for the Amendment:

The protocol is mainly amended to incorporate and implement responses and suggestions made by the United States (US) Food and Drug Administration (FDA).

Non-Substantial Amendment 2 Summary of Changes:

Section # and Name	Description of Change	Brief Rationale
9.4.2 Estimands (Table 9-3)	Text added to include the composite variable strategy of ICE Strategy. Text added to include and specify that robustness of the main estimator will be assessed by using two-dimensional tipping point analyses for FDA submission of Sensitivity Estimator.	Amended following the suggestion from the US FDA.
9.4.5 Handling of Missing Data	Text added to clarify a sensitivity tipping point analysis will be conducted to assess the robustness of results, at both week 52 and week 78.	Amended following the suggestion from the US FDA.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

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1 Protocol Summary

1.1 Synopsis

Protocol 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

Sponsor Protocol No.: RGB-14-101

Study Phase: Phase III

Sponsor: Gedeon Richter Plc.

Rationale:

Gedeon Richter Plc. is developing RGB-14-P (test product) as a biosimilar to Prolia® (reference product) by undertaking a global development programme. The Sponsor is also developing RGB-14-X, as a proposed biosimilar to Xgeva®. Following a step-wise approach subsequent to demonstrating high level of similarity between the proposed biosimilars RGB-14-P and RGB-14-X and the respective reference products Prolia® and Xgeva® at the quality and *in vitro* non-clinical levels, Gedeon Richter Plc., intends to demonstrate clinical comparability by performing comparative pharmacokinetic (PK)/pharmacodynamic (PD) study of RGB-14-X as well as a comparative efficacy and safety study between RGB-14-P and Prolia®. Although the comparative PK/PD study will commence earlier, essentially the two studies will run in parallel.

Objectives and Endpoints:

Objectives	Endpoints
Primary *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	*Efficacy* %CfB in lumbar spine BMD at Week 52
Pharmacodynamics To demonstrate similar pharmacodynamics (AUEC of %CfB in sCTX) of RGB-14-P with US-licensed Prolia® in female participants with postmenopausal osteoporosis (only required for EMA)	*Pharmacodynamics* AUEC of %CfB $sCTX_{0\text{-}m6}$ until Week 26 (secondary for US FDA submission)

Objectives	Endpoints
Secondary	
Efficacy To provide additional comparative efficacy data of RGB-14-P with US-licensed Prolia® in female participants with postmenopausal osteoporosis	*Efficacy* • %CfB in total hip BMD at Weeks 26, 52 and 78 • %CfB in lumbar spine BMD at Weeks 26 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 To provide additional comparative pharmacodynamic data of RGB-14-P with US-licensed Prolia® in female participants with postmenopausal osteoporosis	*Pharmacodynamics* • %CfB in serum P1NP at Weeks 4, 26, 52 and 78 • %CfB in sCTX at Weeks 4, 26, 52 and 78
Safety To compare the safety and tolerability of RGB-14-P with US-licensed Prolia® in female participants with postmenopausal osteoporosis	*Safety* • AE, SAE, 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 To compare the immunogenicity of RGB-14-P with US-licensed Prolia® in female participants with postmenopausal osteoporosis	*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

ADA = anti-drug antibody; AE = adverse event; AUEC = area under the effective curve;
AUEC $sCTX_{0\text{-}m6}$ = AUEC after the first dose until Day 183 of %CfB in serum type I collagen C-telopeptide;
BMD = bone mineral density; %CfB = percent change from baseline; ECG = electrocardiogram;
EMA = European Medicines Agency; FDA = Food and Drug Administration; NAbs = neutralising antibodies;
P1NP = serum procollagen type 1 N-terminal propeptide; SAE = serious adverse event; $sCTX_{0\text{-}m6}$ = serum type I collagen C-telopeptide up to month 6; US = United States

Overall Design:

This is a randomised, double-blind, multicentre, multiple fixed-dose, 2-arm parallel-group study (Main Period) with a Transition Period to assess the efficacy, PD, safety, tolerability and immunogenicity of RGB-14-P compared to US-licensed Prolia® in participants with postmenopausal osteoporosis, in a comparative manner.

Participants will attend a Screening Period within 35 days prior to first dosing. Participants meeting eligibility criteria will enter into the Main Period of the study. The Main Period (52 weeks) consists of Treatment Period 1 (26 weeks) and Treatment Period 2 (26 weeks). The primary endpoint of the study is assessed at the end of the Main Period. The Transition Period consists of Treatment Period 3 (26 weeks), the Transition Period will be applicable to a subset of

participants (see Figure 1–2). Day 1 of Treatment Periods 2 and 3 are the same as Day 183 of the preceding Treatment Period. Timepoints of ambulatory site visits for Treatment Periods 2 and 3 are calculated from the Day 1 of the respective Treatment Period.

All participants will receive the investigational medicinal product (IMP) on 2 occasions (Weeks 0 and 26), on Day 1 of Treatment Periods 1 and 2. Participants continuing to the Transition Period will receive the IMP on a third occasion (Week 52), Day 1 of Treatment Period 3. One Treatment Period will take 6 months (26 weeks, 183 days).

Participants will attend ambulatory site visits on the following timepoints for efficacy, PD, immunogenicity and safety assessment as indicated in the Schedule of Activities (Table 1-1 and Table 1-2).

Main Period:

On Day 1 of Treatment Period 1, prior to dosing, participants will be randomised in a 1:1 ratio to receive either RGB-14-P or Prolia®. Administration of IMP will take place on two occasions in a double-blinded manner (Main Period), on Day 1 of both Treatment Periods 1 and 2 (Weeks 0 and 26).

Visits during the Main Period:

- Days 1, 8, 15, 30, 60, 90, 120 and 150 postdose during Treatment Period 1.
- Days 1, 8, 15, 30 and 90 postdose during Treatment Period 2.

An End-of-Study Visit is planned on Day 183 (Week 52) postdose during Treatment Period 2 for participants not continuing participation in Transition Period. Please see Section 6.7 for additional information on the transition treatment for participants not continuing in Transition Period of study.

Transition Period:

On Day 1 of Treatment Period 3 (Week 52) a total of approximately 198 participants will enter the Transition Period. A subset of approximately 132 participants continuing in the Transition Period who received Prolia® during the Main Period will be re-randomised 1:1 to receive either a dose 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 will continue to receive a dose of RGB-14-P but will also follow the randomisation procedure to maintain blinding.

Visits during the Transition Period:

- Days 1, 8, 15, 30 and 90 postdose during Treatment Period 3.

An End-of-Study Visit is planned on Day 183 (Week 78) postdose during Treatment Period 3. Please see Section 6.7 for additional information on the transition treatment for participants at the end of study.

The estimated duration of the clinical phase for participants in the Main Period from the Screening to the End-of-Study Visit is approximately 13 months and for participants continuing in the Transition period from the Screening Period until the End-of-Study Visit is approximately 19 months.

The primary outcome of this study is determined based on the results of the efficacy analysis at Week 52. To evaluate the efficacy and safety of transitioning from Prolia to RGB-14-P anticipated in a real-world setting, the study will continue up to Week 78. Details of the blinding strategy will be described in the Blinding Maintenance Plan.

The Main Clinical Study Report will be completed based on the data obtained after all participants have completed the Week 52 study visit. The data obtained in the Transition Period will be added as a Final Clinical Study Report.

Disclosure Statement:

This is a randomised, double-blind, multicentre, multiple fixed-dose, 2-arm parallel-group study with a double-blind transition period.

Number of Participants:

Approximately 434 women with postmenopausal osteoporosis are 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 will be stratified by previous use of bisphosphonates and geographical region.

It is planned that 198 participants will continue to participate during the Transition Period, which should ensure to have 180 evaluable participants; approximately 66 participants will continue on the RGB-14-P arm, whereas approximately 132 participants initially assigned to the Prolia® arm will be re-randomised 1:1 whereby approximately 66 participants will continue to receive Prolia® and approximately 66 participants will be switched to RGB-14-P.

Intervention Groups and Duration:

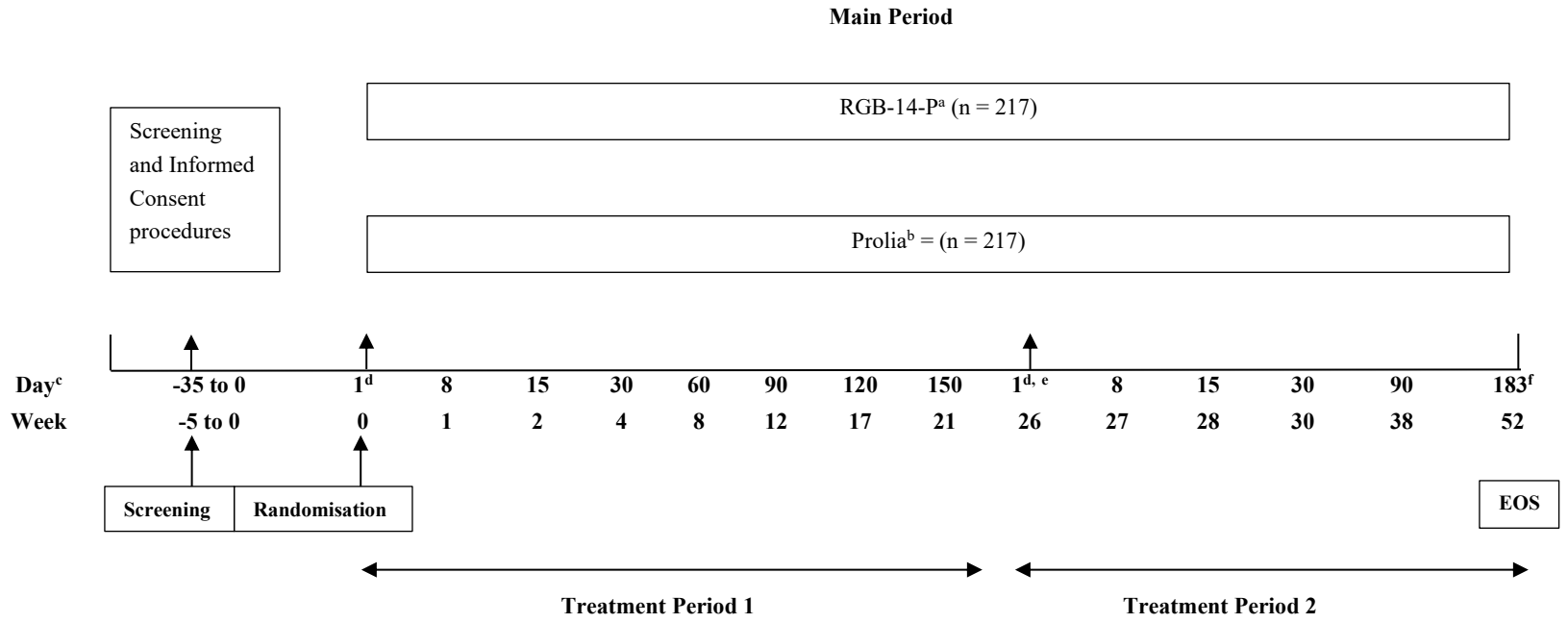
On Day 1 of Treatment Period 1, prior to dosing, participants will be randomised in a 1:1 ratio to receive either RGB-14-P or Prolia®.

Main Period: Participants will receive 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: A subset of approximately 66 participants in the RGB-14-P dose group will follow the randomisation procedure and receive one subcutaneous injection of RGB-14-P, into the thigh, abdomen or upper arm, administered on Day 1 of Treatment Period 3 (Week 52). A subset of approximately 132 participants in the Prolia® dose group will be re-randomised to receive a subcutaneous injection of RGB-14-P or Prolia®, into the thigh, abdomen or upper arm, administered on Day 1 of Treatment Period 3 (Week 52).

1.2 Schema

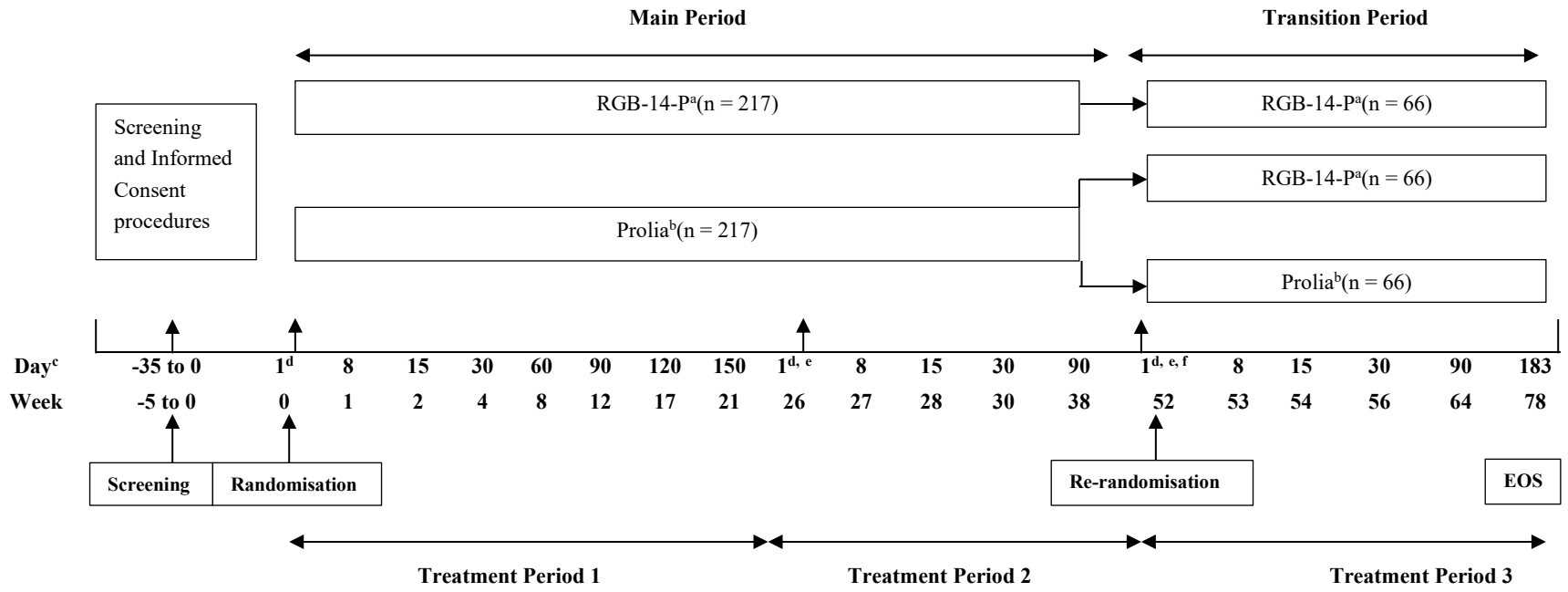
Figure 1–1: Study Design – Main Period only



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 Period 2 is also Day 183 of the preceding treatment period.
f. Participants who will continue to receive the investigational product during Treatment Period 3 will not have an End-of-Study visit on Week 52 but will proceed to Day 1 of Treatment Period 3 (Week 52), see Figure 1–2.

Figure 1–2: Study Design – Main and Transition Period



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 will be 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 will continue to receive a dose of RGB-14-P but will also follow the randomisation procedure to maintain blinding.

1.3 Schedule of Activities (SoA)

Table 1-1 Schedule of Activities (SoA) – Main Period

Study Period	**Days (weeks after first IMP administration)**														
	Screening[b]	**Treatment Period 1**								**Treatment Period 2[c]**					
Day(s)[a] (Week)	**-35 to 0 (-5 to 0)**	**1 (0)**	**8 (1)**	**15 (2)**	**30 (4)**	**60 (8)**	**90 (12)**	**120 (17)**	**150 (21)**	**1 (26)**	**8 (27)**	**15 (28)**	**30 (30)**	**90 (38)**	**183 (52)[c]/ EOS/ ET**
Window Period (Days)			**± 1**	**± 1**	**± 3**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 1**	**± 1**	**± 3**	**± 4**	**± 4**
General Assessments															
Informed Consent	X														
Recording of Demographic Data	X														
Inclusion/Exclusion Criteria Assessment	X	X[d]													
Medical and Surgical History	X														
Weight, Height, BMI[e]	X	X[d]								X[d]					X
Randomisation		X[d]													
IMP Administration		X								X					
Pre-visit Phone Call[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Participant Identification and Visit Reminder Card[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments															
Physical Examination[h]	X	X[d]	X							X[c]					X
Haematology and Clinical Chemistry	X	X[d, i]	X	X[j]	X		X			X[d, i]	X	X[j]	X	X	X
HBV, HCV and HIV Screening	X														
Urinalysis[k]	X	X[d]								X[d]					X
12-lead ECG	X	X[d]								X[d]					X
Vital Signs[l]	X	X[m]	X	X	X	X	X	X	X	X[d]	X	X	X	X	X
Local Tolerance (Skin Examination)		X[n]	X							X[n]	X				
Prior and Concomitant Medication[o]	◄	─	─	─	─	─	─	─	─	─	─	─	─	─	►
Adverse Events	◄	─	─	─	─	─	─	─	─	─	─	─	─	─	►
Medical Device Events[p]		X								X					
Efficacy Assessment															
DXA Scan Assessment	X[q]									X[r]					X
Lateral Spine X-ray	X[q]														X

Study Period	**Days (weeks after first IMP administration)**													
	Screening[b]	**Treatment Period 1**								**Treatment Period 2[c]**					
Day(s)[a] (Week)	**-35 to 0 (-5 to 0)**	**1 (0)**	**8 (1)**	**15 (2)**	**30 (4)**	**60 (8)**	**90 (12)**	**120 (17)**	**150 (21)**	**1 (26)**	**8 (27)**	**15 (28)**	**30 (30)**	**90 (38)**	**183 (52)[c]/ EOS/ ET**
Window Period (Days)			**± 1**	**± 1**	**± 3**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 1**	**± 1**	**± 3**	**± 4**	**± 4**
Immunogenicity Assessment/Serum Drug Concentration Assessment															
Immunogenicity (binding ADAs and NAbs) Sampling		X[d]		X	X					X[d]		X	X		X[d]
Serum Drug Concentration Sampling		X[d]		X	X					X[d]		X	X		X[d]
PD															
PD (Serum CTX) Sampling[s]		X[d]	X	X	X	X	X	X	X	X[d]					X[d]
PD (Serum P1NP) Sampling[s]		X[d]			X					X[d]					X[d]

ADA = anti-drug antibody; BMI = body mass index; CTX = collagen C-telopeptide; DXA = dual energy x-ray absorptiometry; ECG = electrocardiogram; EOS = End-of-Study, ET = early termination; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IMP = investigational medicinal product; NAbs = neutralising antibodies; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamic(s)

a. Day(s) refer to days within Screening or Treatment Period.
b. The Screening visit may be conducted over the Screening period (i.e., more than 1 day can be utilised for Screening during to the Screening period), if necessary, for logistical reasons.
c. Participants who will continue to receive the IMP during Treatment Period 3 will not have an End-of-Study visit on Week 52 but will proceed to Day 1 of Treatment Period 3 (Week 52), see Table 1-2. Please see Section 6.7 for additional information on the transition treatment for participants not continuing in Transition Period of study.
d. Procedure(s)/assessment/blood collection to be performed predose.
e. Height will be measured without shoes at Screening and at all timepoints when BMI is measured.
f. All participants will be contacted by phone 1 day prior to every visit for assessing coronavirus disease 2019 symptoms and signs and if they had any contact with a person who has tested positive for severe acute respiratory syndrome coronavirus 2. During the pre-visit call participants will be reminded of fasting conditions for blood analysis (as applicable).
g. At each visit participants will be provided with a participant identification and visit reminder card. The Investigator must update the visit reminder card at each visit with the details for the next visit.
h. A comprehensive physical examination will include an assessment of general appearance and a review of systems (head, eyes, ears, nose, mouth/oral cavity, throat/neck, thyroid, lymph nodes, dermatologic, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal and neurologic systems).
i. Additional local calcium testing predose may be performed according to local practice or at Investigator's discretion.
j. Albumin-adjusted serum calcium only.
k. Sites will perform a urine dipstick. In case of abnormal results, a urine sample may be sent to the central laboratory for full analysis if deemed necessary by the Investigator. See Appendix 2 (Section 10.2).
l. Vital signs include measurement of blood pressure, pulse and body temperature. Respiratory rate to be assessed at the discretion of the Investigator. Systolic and diastolic blood pressure and pulse measurements will be assessed after the participant has been sitting for at least 5 minutes with back supported and both feet on the floor.

m. Assessments to be done predose and 1 hour postdose.
n. Injection site reaction assessment should be done predose and approximately 1 hour postdose, during this 1 hour period (i.e., from dosing to the injection site assessment) the participant will stay in the clinic for general safety observation. Any further assessment of the injection site or prolonged observation of the participant may be done at the discretion of the Investigator.
o. Compliance with daily calcium and vitamin D intake will be monitored and assessed throughout the study.
p. Information on medical device events (e.g., needle broken, dose not administered properly, syringe condition problem) and medical device events (device incident/deficiency) that caused adverse events or events that led to serious adverse events are to be reported by unblinded site staff in the Product Complaint Form and electronic case report form (adverse events and serious adverse events only) as described in the Addendum to Investigator Manual and the Product Complaint Procedure. A medical device event related to Prolia® will qualify as a device incident and a medical device event related to RGB-14-P will qualify as a device deficiency. See Sections 6.1.2 and 8.5.
q. Dual energy X-ray absorptiometry and lateral X-ray imaging will be done during Screening to determine participant eligibility. Dual energy X-ray absorptiometry and X-ray imaging should be acquired and submitted for central independent review at least 10 days prior to Randomisation.
r. Dual energy X-ray absorptiometry must be performed before dosing at Week 26 and Week 52; however, it can be performed on the same day or in the days before dosing, but within the visit window.
s. A minimum of 8 hours fasting is required prior to blood collection, samples have to be collected in the morning between a window of 7:30 and 10:00 a.m. Participants should refrain from extensive physical exercise for 24 hours before blood collection.

Table 1-2 Schedule of Activities (SoA) – Transition Period

Study Period	**Days (weeks after first IMP administration)**					
	Treatment Period 3					
Day(s)[a] (Week)	**1 (52)b**	**8 (53)**	**15 (54)**	**30 (56)**	**90 (64)**	**183 (78) EOS/ ET**
Window Period (Days)	**± 4**	**± 1**	**± 1**	**± 1**	**± 3**	**± 4**
General Assessments						
Inclusion/Exclusion Criteria Assessment for the Transition Period	X[c]					
Weight, Height, BMI[d]	X[c]					X
Re-randomisation	X[c]					
IMP Administration	X					
Pre-visit Phone Call[e]	X	X	X	X	X	X
Participant Identification and Visit Reminder Card[f]	X	X	X	X	X	X
Safety Assessments						
Physical Examination[g]	X[c]					X
Haematology and Clinical Chemistry	X[c, h]	X	X[i]	X	X	X
Urinalysis[j]	X[c]					X
12-lead ECG	X[c]					X
Vital Signs[k]	X[c]	X	X	X	X	X
Local Tolerance (Skin Examination)	X[l]	X				
Prior and Concomitant Medication[m]	◄	———	———	———	———	►
Adverse Events	◄	———	———	———	———	►
Medical Device Events[n]	X					
Efficacy Assessment						
DXA Scan Assessment	X[o]					X
Lateral Spine X-ray	X					X
Immunogenicity Assessment/Serum Drug Concentration Assessment						
Immunogenicity (binding ADAs and NAbs) Sampling	X[c]		X	X		X
Serum Drug Concentration Sampling	X[c]		X	X		X
PD						
PD (Serum CTX) Sampling[p]	X[c]					X
PD (Serum P1NP) Sampling[p]	X[c]					X

ADA = anti-drug antibody; BMI = body mass index; CTX = collagen C-telopeptide; DXA = dual energy x-ray absorptiometry; ECG = electrocardiogram; EOS = End-of-Study, ET = early termination; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IMP = investigational medicinal product; NAbs = neutralising antibodies; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamic(s)

a. Day(s) refer to days within Screening or Treatment Period.

b. On Day 1 of Treatment Period 3 (Week 52) participants continuing to the Transition Period who received Prolia® during the Main Period will be re-randomised 1:1 to receive either a dose 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 will continue to receive a dose of RGB-14-P but will also follow the randomisation procedure to maintain blinding.
c. Procedure(s)/assessment/blood collection to be performed predose.
d. Height will be measured without shoes at all timepoints when BMI is measured.
e. All participants will be contacted by phone 1 day prior to every visit for assessing coronavirus disease 2019 symptoms and signs and if they had any contact with a person who has tested positive for severe acute respiratory syndrome coronavirus 2. During the pre-visit call participants will be reminded of fasting conditions for blood analysis (as applicable).
f. At each visit participants will be provided with a participant identification and visit reminder card. The Investigator must update the visit reminder card at each visit with the details for the next visit.
g. A comprehensive physical examination will include an assessment of general appearance and a review of systems (head, eyes, ears, nose, mouth/oral cavity, throat/neck, thyroid, lymph nodes, dermatologic, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal and neurologic systems).
h. Additional local calcium testing predose may be performed according to local practice or at Investigator's discretion.
i. Albumin-adjusted serum calcium only.
j. Sites will perform a urine dipstick. In case of abnormal results, a urine sample may be sent to the central laboratory for full analysis if deemed necessary by the Investigator. See Appendix 2 (Section 10.2).
k. Vital signs include measurement of blood pressure, pulse and body temperature. Respiratory rate to be assessed at the discretion of the Investigator. Systolic and diastolic blood pressure and pulse measurements will be assessed after the participant has been sitting for at least 5 minutes with back supported and both feet on the floor.
l. Injection site reaction assessment should be done predose and approximately 1 hour postdose, during this 1 hour period (i.e., from dosing to the injection site assessment) the participant will stay in the clinic for general safety observation. Any further assessment of the injection site or prolonged observation of the participant may be done at the discretion of the Investigator.
m. Compliance with daily calcium and vitamin D intake will be monitored and assessed throughout the study.
n. Information on medical device events (e.g., needle broken, dose not administered properly, syringe condition problem) and medical device events (device incident/deficiency) that caused adverse events or events that led to serious adverse events are to be reported by unblinded site staff in the Product Complaint Form and electronic case report form (adverse events and serious adverse events only) as described in the Addendum to Investigator Manual and the Product Complaint Procedure. A medical device event related to Prolia® will qualify as a device incident and a medical device event related to RGB-14-P will qualify as a device deficiency. See Sections 6.1.2 and 8.5.
o. Dual energy X-ray absorptiometry must be performed before dosing at Week 52; however, it can be performed on the same day or in the days before dosing, but within the visit window.
p. A minimum of 8 hours fasting is required prior to blood collection, samples have to be collected in the morning between a window of 7:30 and 10:00 a.m. Participants should refrain from extensive physical exercise for 24 hours before blood collection.

2 Introduction

RGB-14-P is an investigational medicinal product (IMP) under development intended to be a biosimilar to Prolia®. The Sponsor is also developing RGB-14-X, as a proposed biosimilar to Xgeva®.

Prolia® and Xgeva® are authorised in the European Union (EU) and are licensed in the United States (US). Prolia® and Xgeva® share almost identical formulations and the mechanism of action of denosumab is the same in all approved indications. Therefore, the two products may be regarded as two different strengths of the same product. Consequently, the Sponsor is undertaking a common global development programme for RGB-14-X and RGB-14-P. Subsequently to demonstrating high level of similarity between the proposed biosimilars (RGB-14-X and RGB-14-P) and their respective reference products (Prolia® and Xgeva®) at the quality and *in vitro* non-clinical levels, the Sponsor intends to demonstrate clinical comparability by performing a comparative pharmacokinetic (PK) and pharmacodynamic (PD) study of RGB-14-X and Xgeva® and a comparative efficacy/safety study between RGB-14-P and Prolia®. Although the comparative PK/PD study will commence earlier, essentially the two studies will run in parallel.

For further details regarding the programme please refer to the current version of the Investigator's Brochure (IB) [1].

Since in the comparative efficacy and safety study RGB-14-P will be compared to Prolia® in women with postmenopausal osteoporosis, the subsequent sections will focus on these compounds only.

The active pharmaceutical ingredient in RGB-14-P is denosumab, a fully human immunoglobulin G (IgG)2 monoclonal antibody hetero-tetramer consisting of 2 heavy chains of gamma 1 subclass (488 amino acids per chain) and 2 light chains of the kappa subclass (215 amino acids per chain). It is produced in the mammalian cell line (Chinese hamster ovary cells) by recombinant deoxyribonucleic acid (DNA) technology.

Denosumab belongs to the class of drugs affecting bone structure and mineralisation. The proposed indications for RGB-14-P are the same as those of the reference product, Prolia®.

Therapeutic indications of Prolia according to the Summary of Products Characteristics (SmPC, EU) [2]:

- Treatment of osteoporosis in postmenopausal women and men at increased risk of fractures.
- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.
- Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

Therapeutic indications of Prolia according to the Prescribing Information (US) [3]:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture.
- Treatment of glucocorticoid-induced osteoporosis in men at high risk for fracture.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer.
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

The term “IMP” throughout the protocol, refers to the study drug (RGB-14-P, test product) and/or active comparator (Prolia®, reference product), supplied as a single-dose pre-filled syringe (see Section 6.1). In addition, the terms participant and subject are used interchangeably.

2.1 Background

Osteoporosis is defined as a systemic skeletal disease characterised by low mineral bone mass and microarchitectural deterioration of bone tissue, and increased bone fragility and susceptibility to fracture [4]. Common sites for osteoporotic fracture are the spine, hip, distal forearm and proximal humerus. Fractures resulting from osteoporosis become increasingly common in women after age 55 years and men after age 65 years; resulting in substantial bone-associated morbidities, and increased mortality and health-care costs [5]. As women age the rate of bone turnover increases, resulting in accelerated bone loss because of lack of oestrogen after menopause. Due to its prevalence worldwide, osteoporosis is considered a serious public health concern. Osteoporosis is preventable and treatable, but only a small proportion of those at increased risk for fracture are evaluated and treated.

Receptor activator of nuclear factor kappa-B ligand (RANKL) is a transmembrane or soluble protein, a member of the tumour necrosis factor (TNF) ligand superfamily. It binds to receptor activator of nuclear factor kappa-B (RANK), a member of the TNF receptor superfamily. Receptor activator of nuclear factor kappa-B ligand is also known as TNF related activation induced cytokine (TRANCE), osteoprotegerin ligand (OPGL) and osteoclast differentiation factor (ODF) because of its role in the regulation of bone metabolism. Receptor activator of nuclear factor kappa-B ligand plays and essential role in osteoclast (OC) formation, activity and survival [6]. Osteoclasts are bone-resorbing tissue resident immune cells that are derived from pluripotent haematopoietic stem cells. Osteoclastogenesis requires stimulation by macrophage-colony stimulating factor (M-CSF) and the binding of RANKL, expressed on osteoblasts, to RANK receptor on the OC precursors [7]. Binding of RANKL to the RANK receptor on the cell surface of osteoclasts initiates a complex signalling cascade, which is mediated by TNF receptor associated factor (TRAF)6, TRAF3 and c-Fos transcription factor proteins, which leads to activation of mitogen activated protein kinases (MAPKs), nuclear factor (NK)-κB and activator protein (AP)-1. These signalling pathways result in the translocation of transcriptional activators and subsequently to the expression of numerous effector genes involved in bone resorption [8, 9].

As a "decoy" receptor, denosumab binds with high affinity and specificity to RANKL, preventing activation of RANK on the surface of OC precursors and OCs. Binding of denosumab with RANKL prevents the RANKL/RANK interaction, resulting in impaired OC formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone and cancer-induced bone destruction. Bone strength is mainly determined by the cortical components. Thus, loss of cortical bone contributes to a higher frequency of bone fractures. Denosumab affects not only the thickness of the cortex bus also bone strength, porosity and bone mineral density (BMD) [10].

2.1.1 Summary of Non-clinical Studies

2.1.1.1 *In vitro* Studies

In order to demonstrate analytical similarity between RGB-14-P and Prolia®, extensive physiochemical/structural and *in vitro* biological/functional characterisation has been carried out using a panel of comprehensive state-of-the-art analytical methods. This analytical panel was endorsed by regulatory authorities.

The results of the comprehensive non-clinical *in vitro* PD studies available to date demonstrated comparability between RGB-14-P and its reference medicinal product Prolia®.

For further details please refer to the current version of the IB [1].

2.1.1.2 *In vivo* Studies

Following the current regulatory guidance principles and scientific advices, no comparative *in vivo* toxicological or PD studies have been performed between RGB-14-P and Prolia®. Relevant information on the reference product, Prolia®, is presented based on the public assessment reports, SmPC and US package insert (USPI) of Prolia® [2, 3].

Non-clinical PK studies were conducted in mice, rats and cynomolgus monkeys. While denosumab does not bind to RANKL in mice and rat it recognises and neutralises RANKL in non-human primates.

In rodents the intravenous PK of denosumab were linear over the dose range 0.1 to 10 mg/kg, volume of distribution was similar to plasma volume and clearance was low with long terminal half-lives of 19 days in mice and 11 days in rats. In contrast, clearance was 6- to 15-fold higher in knock-in mice that express a chimeric form of RANKL and in knock-out mice that lack expression of the Fc neonatal receptor.

In the cynomolgus monkey PK were linear over both intravenous and subcutaneous dose range of 1 to 3 mg/kg but were non-liner at doses below 1 mg/kg. The non-linearity in monkeys may reflect that binding of denosumab to RANKL leads to accelerated, but saturable, elimination and that elimination also involves the neonatal Fc receptor (FcRn) and the reticuloendothelial system. After repeated subcutaneous doses of 0.1 to 50 mg/kg in monkey approximately linear PK were reported. Metabolism may be mediated through internalisation followed by intracellular degradation to small peptides and amino acids. Antibodies may be protected from lysosomal degradation through binding to the Fc region of the neonatal receptor FcRn, at acidic pH in the endosome prior to releasing the antibody at the cell surface. The role of FcRn was studied using FcRn knock-out mice. Compared with wild-type mice a much shorter elimination half-live, that was similar to the half-life reported for a murine antibody, was recorded in FcRn knock-out mice and data indicated that FcRn protects denosumab from elimination and so influences tissue distribution.

2.1.1.3 Toxicology

The non-clinical toxicology profile of denosumab is known from registration studies for Prolia®. Denosumab has been shown to be highly specific to RANKL. In single and repeated dose toxicity studies, denosumab doses resulting in 100 to 150 times greater systemic exposure than the recommended human dose had no impact on cardiovascular physiology, male or female

fertility or produced specific target organ toxicity [2]. Moreover, in non-clinical toxicology studies no major differences were revealed regarding the possible immunomodulatory effect of denosumab.

Standard tests to investigate the genotoxicity potential of denosumab have not been evaluated, since such tests are not relevant for this large molecule. Due to its characteristics it is unlikely that denosumab has any potential for genotoxicity.

2.1.2 Summary of Clinical Studies

No clinical studies have been performed to date with RGB-14-P. This is the first clinical study with the test IMP. The Sponsor is also developing RGB-14-X as a biosimilar to Xgeva® and is undertaking a comparative PK/PD study of RGB-14-X and Xgeva®. Both RGB-14-P and RGB-14-X contain the same active ingredient (denosumab). Although the comparative PK/PD study will commence earlier, essentially the two studies will run in parallel.

The PK profile of denosumab in humans is known from relevant information on the reference products, Prolia® and Xgeva®. In healthy participants and postmenopausal women, the PK of denosumab following subcutaneous administration is characterised by first-order absorption, linear distribution to the peripheral compartment and parallel linear and RANKL mediated non-linear elimination.

2.2 Benefit/Risk Assessment

There are potential benefits and risks with the administration of any new investigational medicine as the effects are not fully known. Based on the potential benefit of RGB-14-P, it is being developed for the aforementioned indications (Section 2). Since no clinical studies have been performed to date with RGB-14-P the information in this section is provided based on the SmPC [2] and USPI [3] of Prolia®.

Postmenopausal osteoporotic women participating in the study are expected to directly benefit from the treatment with the IMPs. In addition, the availability of biosimilars on the market will improve patient access to a highly effective treatment benefiting a wider community.

2.2.1 Risk Assessment

Based on current available data, it is anticipated that the adverse event (AE) profile of RGB-14-P will be similar to that of Prolia®, therefore the same contraindications, precautions and warnings for Prolia® will also apply to RGB-14-P.

The adverse reactions associated with Prolia® are as follows [2]:

- **Very common (≥ 1/10):** pain in limbs, musculoskeletal pain.
- **Common (≥ 1/100 to < 1/10):** urinary tract infection, upper respiratory tract infection, sciatica, constipation, abdominal discomfort, rash, eczema, alopecia.
- **Uncommon (≥ 1/1000 to < 1/100):** diverticulitis, cellulitis, ear infections, lichenoid drug eruptions.
- **Rare (≥ 1/10000 to < 1/1000):** drug hypersensitivity, anaphylactic reaction, hypocalcaemia, osteonecrosis of the jaw (ONJ), atypical femoral fractures.
- **Very rare (< 1/10000):** hypersensitivity vasculitis.
- **Not known:** osteonecrosis of the external auditory canal.

In postmenopausal women with osteoporosis the most common adverse reactions (> 5% and more common than placebo) included back pain, pain in extremities, hypercholesterolemia, musculoskeletal pain, cystitis and vertigo. Pancreatitis has also been reported in clinical trials [3].

Adverse reactions reported in ≥ 2% of patients with osteoporosis and more frequently than in placebo-treated patients with Prolia® include; anaemia, angina pectoris, atrial fibrillation, upper abdominal pain, flatulence, gastroesophageal reflux disease, peripheral oedema, asthenia, vertigo, upper respiratory tract infection, pneumonia, pharyngitis, herpes zoster, bone pain, myalgia, spinal osteoarthritis, sciatica, insomnia, rash, pruritus [3].

Other adverse reactions reported in < 2% of patients with osteoporosis and more frequently than in placebo-treated patients with Prolia® include: hypocalcaemia, serious infections in the abdomen, serious urinary tract infections, serious ear infections, endocarditis, erysipelas, cellulitis, ONJ, atypical subtrochanteric and diaphyseal femoral fractures [3].

Vasculitis and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome has also been reported in postmarketing experience.

A detailed description of adverse reactions is provided in the SmPC [2] and USPI [3] of Prolia®.

The protocol has been designed to minimise the risk to the study participants. Special warnings and precautions for the use of denosumab are reflected in strict inclusion and exclusion criteria for this study. From Day 1 through the End-of-Study/Early Termination Visit, supplementation

of at least 1000 mg calcium and at least 800 IU vitamin D3 daily will be administered to all participants in this study.

Participants will be monitored to detect AEs during the study and followed appropriately to ensure the resolution of AEs. Safety assessments will consist of the regular monitoring of haematology, clinical chemistry, urinalysis, regular measurements of vital signs, physical examinations, injection site reactions and fracture assessments, electrocardiogram (ECG) as well as monitoring and recording of AEs and serious adverse events (SAEs).

Participants might also experience procedural complications (e.g., blood draws, slight skin irritation from the adhesive on the ECG electrodes, device incident or device deficiency AEs).

No serious adverse events are considered expected by the Sponsor for the purpose of expedited reporting of suspected unexpected serious adverse reactions (SUSARs) and identification of SUSARs in the "Cumulative summary tabulation of serious adverse reactions" in the development safety update report for the IMP.

Risk Assessment for Coronavirus Disease 2019 Pandemic

The IMP is a human monoclonal IgG2 antibody targeting and binding RANKL and is believed not to cause immune suppression.

The risk of exposure to infected people cannot be completely excluded as the participants may need to expose themselves to public areas (e.g., commute to the site) and have additional human contact (e.g., with site staff and other participants of the clinical study).

Measures to mitigate the additional risks caused by coronavirus disease 2019 (COVID-19) are:

- This study is going to start enrolling only when the Sponsor and contract research organisation (CRO) in collaboration deem it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic preventing safe study start are lifted by the local authorities.
- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.
- Participants will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnoea, sore throat, fatigue and loss of sense of taste or smell throughout the study. Once clinical signs of infection are reported by participants, the Investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If

not, AEs and concomitant medications will be obtained via phone calls. Body temperature measurements during visits will be implemented.

- In case of suspected COVID-19 infection the Investigator will follow the local regulations. Dosing with the IMP is permitted only if COVID-19 could be ruled out. Once diagnosis of COVID-19 was established, the Investigator should contact the Medical Monitor to discuss if the participant can continue in the study. The next dose administration should be considered after recovery and after fulfilling local requirements.
- Confirmation of COVID-19 infection by optional laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests and on Investigator's discretion. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) analysis can be performed at Screening and at any time point as deemed required by local regulation or by the Investigator. It is the Investigator's responsibility to adhere to local regulations and requirements for COVID-19 testing of asymptomatic as well as symptomatic participants.
- The probability of virus transmission will be controlled as much as possible by:
  - Advice for participant to adhere to local requirements for reduction of the public exposure while ambulatory.
  - All participants are contacted by phone one day prior to every visit for assessing COVID-19 symptoms and signs and are informed on the possibility of attending the site as per local requirements. In addition, participants are asked for any contact with a person who has tested positive for SARS-CoV-2. If applicable, participants will be referred to the local health care system for further follow-up and treatment.
  - Physical distancing and person-to-person contact restrictions will be applied during site visits and in-house confinement (if applicable).
  - Where physical distancing is not possible personal protective equipment will be used by study participant (surgical face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the Investigators and site staff and guided by local requirements.

2.2.2 Benefit Assessment

Denosumab is marketed in the EU and US under the trade names Prolia® and Xgeva®. Prolia® was approved in 2010 for osteoporosis in postmenopausal women and in men at increased risk of fractures, for the treatment of bone loss associated with hormone ablation in men with prostate

cancer at increased risk of fractures and for the treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients with increased risk of fracture.

The efficacy and safety of denosumab have been demonstrated in many double-blind and open-label trials for postmenopausal women [11, 12, 13, 14]. In osteoporosis, it is proven to increase BMD and protect bones from fracture. Since the authorisation extensive experience has been gained about Prolia® further substantiating its safe and efficacious use which has been associated with a positive benefit/risk ratio in the target population.

Postmenopausal osteoporotic women participating in this study are expected to directly benefit from the denosumab effect of decreasing fracture risk. In addition, they might also derive some health benefits from participating in the study through the rigorous medical assessments performed at the time of Screening and throughout the study. Since biosimilar products improve patient access to highly effective treatments, their development and subsequent availability on the market come with significant socioeconomic benefits as well.

2.2.3 Overall Benefit: Risk Conclusion

Since its marketing authorisation, extensive experience has been gained with Prolia® further substantiating its safety and efficacious use which has been associated with a positive/risk ratio in the target population.

RGB-14-P has a potential to reduce osteoporosis and improve quality of life in study participants. This study in women with postmenopausal osteoporosis will continue to evaluate the safety profile of RGB-14-P.

RGB-14-P is expected to have a similar clinical outcome to Prolia® based on the physiochemical and biological similarity.

Taking into account the measures taken to minimise risk to participants participating in this study, the potential risks identified in association with RGB-14-P are justified by the anticipated benefits that may be afforded to participants with osteoporosis.

More detailed information about the known and expected benefits, risks and AE profile can be found in the current version of the IB [1].

3 Objectives and Endpoints

The study objectives and endpoints are summarised in Table 3-1.

Table 3-1 Objectives and Endpoints

Objectives	Endpoints
Primary *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	*Efficacy* %CfB in lumbar spine BMD at Week 52
Pharmacodynamics To demonstrate similar pharmacodynamics (AUEC of %CfB in sCTX) of RGB-14-P with US-licensed Prolia® in female participants with postmenopausal osteoporosis (only required for EMA)	*Pharmacodynamics* AUEC of %CfB $sCTX_{0\text{-}m6}$ until Week 26 (secondary for US FDA submission)
Secondary *Efficacy* To provide additional comparative efficacy data of RGB-14-P with US-licensed Prolia® in female participants with postmenopausal osteoporosis	*Efficacy* • %CfB in total hip BMD at Weeks 26, 52 and 78 • %CfB in lumbar spine BMD at Weeks 26 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 To provide additional comparative pharmacodynamic data of RGB-14-P with US-licensed Prolia® in female participants with postmenopausal osteoporosis	*Pharmacodynamics* • %CfB in serum P1NP at Weeks 4, 26, 52 and 78 • %CfB in sCTX at Weeks 4, 26, 52 and 78
Safety To compare the safety and tolerability of RGB-14-P with US-licensed Prolia® in female participants with postmenopausal osteoporosis	*Safety* • AE, SAE, 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 To compare the immunogenicity of RGB-14-P with US-licensed Prolia® in female participants with postmenopausal osteoporosis	*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

ADA = anti-drug antibody; AE = adverse event; AUEC = area under the effective curve; AUEC $sCTX_{0\text{-}m6}$ = AUEC after the first dose until Day 183 of %CfB in serum type I collagen C-telopeptide; BMD = bone mineral density; %CfB = percent change from baseline; ECG = electrocardiogram; EMA = European Medicines Agency; FDA = Food and Drug Administration; NAbs = neutralising antibodies; P1NP = serum procollagen type 1 N-terminal propeptide; SAE = serious adverse event; $sCTX_{0\text{-}m6}$ = serum type I collagen C-telopeptide up to month 6; US = United States

4 Study Design

4.1 Overall Design

This is a randomised, double-blind, multicentre, multiple fixed-dose, 2-arm parallel-group study (Main Period) with a Transition Period to assess the efficacy, PD, safety, tolerability and immunogenicity of RGB-14-P compared to US-licensed Prolia® in participants with postmenopausal osteoporosis, in a comparative manner.

Participants will attend a Screening Period within 35 days prior to first dosing. Participants meeting eligibility criteria will enter into the Main Period of the study. The Main Period (52 weeks) consists of Treatment Period 1 (26 weeks) and Treatment Period 2 (26 weeks). The primary endpoint of the study is assessed at the end of the Main Period. The Transition Period consists of Treatment Period 3 (26 weeks), the Transition Period will be applicable to a subset of participants (see Figure 1–2). Day 1 of Treatment Periods 2 and 3 are the same as Day 183 of the preceding Treatment Period. Timepoints of ambulatory site visits for Treatment Periods 2 and 3 are calculated from the Day 1 of the respective Treatment Period.

All participants will receive the IMP on 2 occasions (Weeks 0 and 26), on Day 1 of Treatment Periods 1 and 2. Participants continuing to the Transition Period will receive the IMP on a third occasion (Week 52), Day 1 of Treatment Period 3. One Treatment Period will take 6 months (26 weeks, 183 days).

Participants will attend ambulatory site visits on the following timepoints for efficacy, PD, immunogenicity and safety assessment as indicated in the Schedule of Activities (SoA) (Table 1-1 and Table 1-2).

Main Period:

On Day 1 of Treatment Period 1, prior to dosing, participants will be randomised in a 1:1 ratio to receive either RGB-14-P or Prolia®. Administration of IMP will take place on two occasions in a double-blinded manner (Main Period), on Day 1 of both Treatment Periods 1 and 2 (Weeks 0 and 26).

Visits during the Main Period:

- Days 1, 8, 15, 30, 60, 90, 120 and 150 postdose during Treatment Period 1.
- Days 1, 8, 15, 30 and 90 postdose during Treatment Period 2.

An End-of-Study Visit is planned on Day 183 (Week 52) during Treatment Period 2 for participants not continuing participation in the Transition Period. Please see Section 6.7 for additional information on the transition treatment for participants not continuing in Transition Period of study.

Transition Period:

On Day 1 of Treatment Period 3 (Week 52) a total of approximately 198 participants will enter the Transition Period. A subset of approximately 132 participants continuing in the Transition Period who received Prolia® during the Main Period will 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 will continue to receive a dose of RGB-14-P but will also follow the randomisation procedure to maintain blinding (see Section 9.2).

Visits during the Transition Period:

- Days 1, 8, 15, 30 and 90 postdose during Treatment Period 3.

An End-of-Study Visit is planned on Day 183 (Week 78) postdose during Treatment Period 3. Please see Section 6.7 for additional information on the transition treatment for participants at the end of the study.

The estimated duration of the clinical phase for participants in the Main Period from the Screening to the End-of-Study Visit is approximately 13 months and for participants continuing in the Transition period from the Screening Period until the End-of-Study Visit is approximately 19 months.

The primary outcome of this study is determined based on the results of the efficacy analysis at Week 52. To evaluate the efficacy and safety of transitioning from Prolia® to RGB-14-P anticipated in a real-world setting, the study will continue up to Week 78.

Details of the blinding strategy will be described in the Blinding Maintenance Plan.

The Main Clinical Study Report will be completed based on the data obtained after all participants have completed the Week 52 study visit. The data obtained in the Transition Period will be added as a Final Clinical Study Report.

4.2 Scientific Rationale for Study Design

The clinical development programme for RGB-14-P follows the scientific and ethical principles as stated in the European Medicines Agency (EMA) regulations for biosimilar products: CHMP/437/04 Rev. 1., EMEA/CHMP/BMWP/42832/2005 Rev. 1, EMEA/CHMP/BMWP/14327/2006 Rev. 1, EMA/CHMP/BMWP/86289/2010, EMA/CHMP/BMWP/403543/201 and follows the Food and Drug Administration (FDA) regulations (Scientific Considerations in Demonstrating Biosimilarity to a Reference Product) and is designed based on Scientific Advices received from Paul-Ehrlich-Institut, the EMA and the FDA.

This study forms part of the clinical development programme and is aimed to assess the efficacy and safety of RGB-14-P compared to Prolia® in women with postmenopausal osteoporosis as a randomised, double-blind, multicentre phase III study. Of all therapeutic indications of Prolia® postmenopausal osteoporosis is considered to be the most sensitive one as postmenopausal osteoporotic females are exempt from underlying disease conditions and concomitant medications that might influence the efficacy and the safety of the IMPs consequently, they represent the most homogenous study population.

In light of the outcome of a follow-up Scientific Advice at EMA, demonstration of analytical comparability between the US- and the EU-sourced reference materials serves as an adequate bridge, allowing Gedeon Richter Plc. to utilise only US-sourced reference material throughout the clinical development.

The safety assessments for the study are accepted measures for ensuring safety of participants during a clinical study. The sample size is considered adequate and sufficient to allow for a meaningful comparison between RGB-14-P and Prolia®. The rationale for dose selection is discussed in Section 4.3. The study design is deemed appropriate for conduct during the COVID-19 pandemic.

4.3 Justification for Dose

The approved dose for Prolia® is 60 mg administered every 6 months as a subcutaneous injection in the upper arm, upper thigh or abdomen [3]. The dose, frequency and route of administration of RGB-14-P have been selected to be consistent with that of Prolia® for the therapy of women with postmenopausal osteoporosis, as described in the Prolia® SmPC and USPI [2, 3].

4.4 End of Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the SoA (Table 1-2) for the last participant in the study.

5 Study Population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

The study population will consist of approximately 434 female participants with postmenopausal osteoporosis. Postmenopausal osteoporotic females are exempt from underlying disease conditions and concomitant medications that might influence the efficacy and the safety of the IMPs consequently they represent the most homogeneous and as such the most sensitive study population.

Participants must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant is ≥ 60 to ≤ 90 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participant is an ambulatory postmenopausal woman, diagnosed with osteoporosis, able to walk and not bedridden. A woman is considered postmenopausal if she meets any of the following criteria:
   a. Has 12 months of spontaneous amenorrhea without an alternative medical cause with serum follicle-stimulating hormone (FSH) levels falling in the normal postmenopausal range at the central laboratory at the time of the Screening Period.
   b. Female participant underwent bilateral oophorectomy (with or without hysterectomy) at least 6 weeks prior to the Screening Period.
3. Participant has an absolute 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 2 lumbar vertebrae (from L1 to L4) must be evaluable by DXA.

Weight

4. Participant has body weight ≥ 50 and ≤ 90 kg at the Screening Period.

Informed Consent

5. Participant is willing and able to give signed informed consent as described in Appendix 1 (Section 10.1.3) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
6. Participant has provided informed consent prior to any study-specific activities/procedures.

Participant must meet the following criteria to be enrolled in the Transition Period:

7. Have been enrolled, received both doses of IMP, adequately complied with the protocol and completed the scheduled Main Period (up to Week 52) of the RGB-14-101 study.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participant has a history and/or presence of a severe or more than two moderate vertebral fractures as determined by central reading of lateral spine X-ray during the Screening Period.
2. Participant has a history and/or presence of hip fracture.
3. Participant has a history and/or presence of atypical femur fracture.
4. Participant presents with an active healing fracture according to the assessment of the Investigator.
5. Participant has a bilateral hip replacement (unilateral is allowed if the other hip is evaluable with DXA).
6. Participant has a vitamin D deficiency (defined as a serum 25 hydroxyvitamin D level < 50 nmol/L [20 ng/mL]), the assessment may be repeated once after vitamin D supplementation (including calcitriol). Appropriate vitamin D dosing in addition to vitamin D supplementation is permitted at the discretion of the Investigator during the Screening Period.
7. Participant has hypocalcaemia or hypercalcaemia (defined as albumin-adjusted serum calcium for hypocalcaemia < 2.1 mmol/L [8.4 mg/dL] or for hypercalcaemia > 2.62 mmol/L [10.6 mg/dL]) at the Screening Period, the assessment may be repeated once in the case of hypercalcaemia.

8. Participant has a history and/or presence of bone metastases, renal osteodystrophy, osteomyelitis, any metabolic, endocrine or traumatic bone disease (except postmenopausal osteoporosis) that may interfere with the interpretation of the results, e.g., Paget's disease, rheumatoid arthritis, ankylosing spondylitis, osteomalacia, osteogenesis imperfecta, acromegaly, achondroplasia, osteopetrosis, Cushing's disease, hyperprolactinemia or malabsorption syndrome. Participants with history of childhood rickets may be eligible provided that the condition had been cured before the age of 25 years.
9. Participant has a current uncontrolled status of hypothyroidism or hyperthyroidism. Uncontrolled means if any of the following are present: a) clinical signs and symptoms of active hyper/hypothyroidism, b) thyroid-stimulating hormone (TSH) is below the reference range of the central laboratory, c) TSH is above the reference range of the central laboratory which necessitates the initiation of treatment or if the treatment is already given it is deemed insufficient by the Investigator considering the age of the participant.
10. Participant has a history (within 5 years prior to Screening) and/or current hypoparathyroidism or hyperparathyroidism other than clinically not significant secondary hyperparathyroidism.
11. Participant has had major surgery within 8 weeks prior to the Screening Period or planned, anticipated major surgery during the study.
12. Participant has malignancy within 5 years before Screening (except completely cured in situ cervical carcinoma or non-metastatic squamous or basal cell carcinoma of the skin).
13. Participant has a history and/or presence of significant cardiac disease or ECG abnormalities indicating significant risk for participating in the study as judged by the Investigator.
14. Participant has a known intolerance or malabsorption of calcium or vitamin D supplements.
15. Participant has a known hypersensitivity (including severe allergic reaction) to monoclonal antibodies or a history of systemic hypersensitivity to any components of the IMPs.
16. Participant shows contraindications to denosumab therapy (e.g., hypocalcaemia), or calcium or vitamin D supplementation before starting IMP administration.
17. Participant has a latex allergy.

18. Participant has a history and/or presence of ONJ or risk factors for ONJ such as heavy smoking, invasive dental procedures without complete healing or planned during the study (e.g., tooth extraction, dental implants, oral surgery), planned radiotherapy to head and neck, poor oral hygiene, poor fitting dentures, periodontal, and/or pre-existing dental disease checked as required by local guidelines and if deemed to be at unacceptable risk for denosumab use by the Investigator.
19. Participant has history and/or presence of osteonecrosis of the external auditory canal.

Prior/Concomitant Therapy

20. Participant requiring ongoing use of any osteoporosis treatment (other than calcium and vitamin D supplements).
21. Participant has previously received denosumab or biosimilar denosumab.
22. Participant has previously received the following medicines:
    a. Romosozumab (dose received at any time).
    b. Cathepsin K inhibitors (dose received at any time).
    c. Strontium or fluoride (for osteoporosis) (dose received at any time).
    d. Any investigational medicinal product not specified in the protocol for treatment of osteoporosis (dose received at any time).
    e. Intravenous bisphosphonates (dose received within 5 years prior to the Screening Period).
    f. Oral bisphosphonates (more than 3 years of cumulative use prior to the Screening Period or any dose received within 1 year prior to the Screening Period).
    g. Teriparatide, abaloparatide or any parathyroid hormone (PTH) analogues (dose received within 1 year prior to the Screening Period).
    h. Tibolone, oral or topical (e.g., transdermal, intravaginal) oestrogen, antioestrogens, selective oestrogen receptor modulators (SERMs) and aromatase-inhibitors (dose received within 1 year prior to the Screening Period).
    i. Calcitonin or its derivates and calcimimetics (such as cinacalcet or etelcacetide) (dose received within 6 months prior to the Screening Period).
    j. Systemic glucocorticosteroids (≥ 5 mg prednisone or equivalent per day for ≥ 10 days or a total cumulative dose of ≥ 50 mg) within the past 3 months prior to the Screening Period. Topical and inhaled glucocorticosteroids are allowed.

k. Other bone active drugs including heparin (also low molecular weight heparins), vitamin K (supplementation or therapeutic dose), vitamin K antagonists (e.g., warfarin, acenocumarol), emtricitabine, tenofovir, adefovir, anti-convulsants (with the exception of benzodiazepines, gabapentin and pregabalin), systemic ketoconazole, adrenocorticotropic hormone (ACTH), lithium, protease inhibitors, gonadotropin-releasing hormone (GnRH) agonists or anabolic steroids within the past 3 months prior to the Screening Period.

Prior/Concurrent Clinical Study Experience

23. Participant is receiving or has received any investigational drug (or is currently using an investigational device) within 3 months before receiving IMP, or at least 10 times the respective elimination half-life (whichever period is longer).

Diagnostic Assessments

24. Participant has weight or girth measurements which may preclude accurate DXA measurements in Investigator's opinion.
25. Participant has inadequate renal and hepatic function at the Screening Period defined as patient on dialysis or estimated glomerular filtration rate (eGFR) < 30 mL/min (calculated using the modification of diet in renal disease [MDRD] formula) and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2 ×upper limit of normal (ULN) or total bilirubin ≥ 1.5 ×ULN (except in Gilbert's syndrome, where the total bilirubin is accepted if ≤ 2.5 × ULN).
26. Participant presents with clinically significant leukopenia, neutropenia or anaemia as judged by the Investigator; the assessment may be repeated once if the condition is deemed to be temporary by the Investigator.
27. Participant has an active infection, including, but not limited to SARS-CoV-2, hepatitis B/hepatitis B surface antigen (HBsAg) positivity and/or participant who has anti-hepatitis B core antigen (HBcAg) positivity with anti-HBsAg negativity, hepatitis C and human immunodeficiency virus infections during the Screening Period.

Other Exclusions

28. Current or past alcohol or drug abuse.
29. Any other clinically significant disorder/condition/disease or laboratory abnormality that in the opinion of the Investigator would pose a risk to participant safety or interfere with the study evaluation, procedures or completion.

30. Participant is pregnant at Screening or does not agree to not breastfeed starting at Screening and throughout the study period and for 5 months after final study treatment administration.

Participant meeting the following criteria must not be enrolled in the Transition Period:

31. Treatment continuation in the study is against the best interest of the participant as deemed by the Investigator.

5.3 Lifestyle Considerations and Restrictions

1. Participant must have blood samples taken for each PD analysis (bone turnover markers [serum type I collagen C-telopeptide (sCTX) and procollagen type 1 N-terminal propeptide (P1NP)]) after a minimum of 8 hours fasting. During the pre-visit phone call participants will be reminded of fasting conditions for blood analysis (as applicable).
2. Blood for PD sampling must be collected in the morning between 07:30 and 10:00 am.
3. Participants should refrain from extensive physical exercise for 24 hours before each blood collection for PD analysis.
4. On the day of Baseline PD assessment (Treatment Period 1, Day 1 [Week 0]), calcium should not be given before the PD blood sampling.
5. Participants are encouraged to maintain good oral hygiene and receive routine dental check-ups. During the study treatment phase invasive dental procedures should be performed only after careful consideration (if required for AE/SAE management).
6. Participants should seek prompt medical attention if they develop signs or symptoms of OJN, hypocalcaemia, infections, dermatological reaction or hypersensitivity.
7. Participants are encouraged to adhere to country level and/or local COVID-19 regulations for prevention and monitoring of pandemic. The guidance from Competent Authorities may continue to evolve, Investigators are encouraged to check for updates regularly and provide participants with appropriate instructions. Please see Section 2.2.1 and Appendix 4 (Section 10.4) for additional information.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised. Eligible but surplus participants will not be screen failures. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information

includes demography, reason for screen failure (e.g., eligibility requirements failed), and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for rescreening, only once, unless participants screen fail due to safety reasons which are significant and not likely to resolve, or if participation in the study would unacceptably jeopardise the safety of the participant as deemed by the Investigator. In all cases without exception the rescreening is conditional upon approval of the Medical Monitor i.e., prior to rescreening, the Investigator must contact the Medical Monitor to discuss the rescreening on a case-by-case basis. All screening procedures will be repeated during rescreening with the following exceptions: DXA, if it is within 5 weeks of the initial scan and lateral spine X-ray, if it is within 3 months of the initial scan. In the event of rescreening the data gathered during rescreening should prevail.

In the case of failure to meet criteria for vitamin D or calcium (Section 5.2, exclusion criteria 6 and 7, respectively), vitamin D and calcium testing may be repeated (i.e., the participant is retested for those parameters) once during the screening period without rescreening the participant provided that the other criteria are met. These retest cases will not be considered as rescreening.

5.4.1 Screening and Enrolment Log

All screened participants will be assigned a unique enrolment number which is study specific. Enrolled participants who drop out of the clinical study before randomisation will retain their enrolment number. The participant's enrolment will be recorded in the Screening and Enrolment Log. After enrolment, prior to dosing, participants will be randomised and receive a randomisation number. Prior to dosing in Treatment Period 3, participants will be re-randomised and receive a second randomisation number. Participant numbers must not be re-used for different participants.

6 Study Treatments

Study treatment (IMP) is defined as the test product (RGB-14-P) and the reference product (US-sourced Prolia®), which are collectively referred to as IMP throughout the protocol. The IMP is to be administered to the study participants according to the study protocol during this study.

In light of the outcome of a follow-up scientific advice at the EMA, demonstration of analytical comparability between the US- and EU-sourced reference products serves as an adequate bridge allowing the Sponsor to utilise only the US-sourced reference product throughout the clinical development.

6.1 Study Treatments Administered

The study treatments that will be administered in this study are outlined in Table 6-1.

Table 6-1 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(s):	60 mg	60 mg
Dosage Level(s):	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.
Dosing Instructions:	Main Period: On Day 1 of Treatment Period 1, prior to dosing, participants will be randomised in a 1:1 ratio to receive either RGB-14-P or Prolia®. Participants will receive 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 will follow the randomisation procedure and receive 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 will be re-randomised to receive either one subcutaneous injection of RGB-14-P or Prolia® into the thigh, abdomen or upper arm. IMP will be administered in the morning.	
Device Description:	IMP will be 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 will be 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.

Arm Name:	RGB-14-P	Prolia®
Storage:	IMP will be stored in a secure area at 2 to 8°C (35.6 to 46.4°F) and in accordance with applicable regulatory requirements.	IMP will be stored in a secure area at 2 to 8°C (35.6 to 46.4°F) and in accordance with applicable regulatory requirements.

IMP = investigational medicinal product; US = United States

Please see Section 6.5.2 for information on calcium and vitamin D administration.

6.1.1 Study Treatment Devices

6.1.1.1 RGB-14-P

RGB-14-P is supplied in a single-use disposable, handheld 1 mL long pre-filled syringe with a staked-in needle (27 gauge × ½ inch). In order to prevent accidental needlesticks, the syringe is assembled with a needle guard. Further information on packaging, labelling, storage, handling and administration of RGB-14-P can be found in the Investigator Manual. Further description on the device will be provided in the Addendum to Investigator Manual.

6.1.1.2 Prolia®

US-licensed Prolia® is supplied in a single-use disposable, handheld 1 mL long pre-filled syringe with a staked-in needle (27 gauge × ½ inch). In order to prevent accidental needlesticks, the syringe is assembled with a needle guard. Further information on packaging, labelling, storage, handling and administration of Prolia® can be found in the Investigator Manual. Further description on the device will be provided in the Addendum to Investigator Manual.

6.1.2 Medical Device Events

Medical device events related to Prolia® will qualify as device incidents (any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effects). Medical device events related to RGB-14-P will qualify as device deficiencies (any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer).

Information on a device incident or device deficiency (e.g., needle broken, dose not administered properly, syringe condition problem) will be reported in the Product Complaint Form by unblinded site staff. The Addendum to Investigator Manual and Product Complaint Form should only be accessible to unblinded staff. Details pertaining to processing and reporting medical

device events are described in the Addendum to Investigator Manual and the Product Complaint Procedure.

Device incident or device deficiency that cause site staff related injury will be reported in the Product Complaint Form by unblinded site staff as it is described in the Addendum to Investigator Manual and the Product Complaint Procedure.

Adverse events and SAEs caused by device incident or deficiency should be collected and reported in the electronic case report form (eCRF) according to Safety Procedures (see Sections 8.5 and 10.3), in addition, a Product Complaint Form should be completed and reported by unblinded site staff as it is described in the Addendum to Investigator Manual and the Product Complaint Procedure.

6.2 Preparation, Handling, Storage, and Accountability

The Investigator or designee must maintain a log to confirm appropriate temperature conditions have been maintained during transit for all IMP received and any discrepancies are reported and resolved before use of the IMP.

Only participants enrolled in the study may receive IMP and only authorised site staff may supply or administer IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IMP are provided in the IMP handling instructions.

6.3 Measures to Minimise Bias: Randomisation and Blinding

6.3.1 Randomisation

At randomisation (Treatment Period 1, Day 1) all eligible participants will be randomised via Interactive Response Technology (IRT) to one of the treatment groups. The Investigator or his/her delegate will contact the IRT after confirming that the participant fulfils all the inclusion/exclusion criteria and Parexel Medical Monitor has no objection against inclusion of the participant. The IRT will assign a randomisation number and will specify a unique medication number for the first package of IMP to be dispensed to the participant.

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

6.3.2 Re-randomisation and Participant Subset in Transition Period

A subset of approximately 198 participants who complete the Main Period (Treatment Periods 1 and 2) and continue participation in Treatment Period 3, will be allocated treatment for Treatment Period 3 at the beginning of Treatment Period 3 via IRT in a blinded fashion. Enrolment during the Transition Period will be consecutive (the next eligible participant will be enrolled). A subset of approximately 132 participants in the Treatment Periods 1 and 2 Prolia® dose group will be re-randomised in a 1:1 ratio to either transition to receive RGB-14-P in Treatment Period 3 or continue on Prolia®. A subset of approximately 66 participants originally randomised to RGB-14-P in Treatment Periods 1 and 2 will automatically continue on RGB-14-P in Treatment Period 3 but this will also be performed via the IRT system to maintain the blind of treatment assignment (i.e., all participants in the RGB-14-P dose group will be re-randomised to continue on RGB-14-P during Treatment Period 3).

Investigational medicinal product will be administered at the study visits summarised in Section 6.1.

6.3.3 Blinding and Breaking the Blind

A double-blind design will be used during the Main and Transition Periods to avoid any bias that may result from the Sponsor or staff being aware of the treatment sequence assignment for an individual participant, e.g., assigning relationship of AEs to IMP, bioanalysis of samples, exclusion of bioanalytical data from the evaluation and determination of analysis populations.

During the Main Period, all participants and site personnel (except for delegated unblinded pharmacy staff, unblinded healthcare professional responsible for IMP administration), Parexel personnel (except for the logistics team, randomisation biostatistician and unblinded monitor) as well as subcontracted laboratory personnel will be blinded to the study treatment. The Sponsor, including the bioanalytical laboratory, will be blinded to the assignment of study treatment during the 12-month double-blinded phase (Main Period). However, the Sponsor's Clinical Safety Unit, Clinical Good Manufacturing Practice Quality Assurance and Qualified Person

colleagues of Total Quality Management Directorate and Regulatory Science Division Medical Device Experts will serve as unblinded personnel throughout the whole study for safety reporting purposes. Part of Parexel's personnel will be unblinded after database lock for the 12-month Main Period and as such will not be in direct contact with the sites or involved in any treatment decisions during the Transition Period.

During the 6-month Transition Period, participants, investigators and blinded site staff, as well as Parexel personnel in direct contact with the sites will remain blinded to the treatment assignment. Additionally, the Sponsor operational team, including the bioanalytical laboratory, will remain blinded to the assignment of study treatment until database lock for the 6-month Transition Period.

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

If a device incident or device deficiency cause an AE or SAE during the study the unblinded study team member needs to inform the Principal Investigator without providing information which may disclose the treatment arm. The unblinded team member will complete the Product Complaint Form and share with the unblinded clinical team at Parexel. In any circumstances, the unblinded study team members should not disclose any information that may lead to unblinding to treatment allocation.

If an SAE occurs during the study that meets the criteria for expedited reporting (i.e., is a SUSAR) as assessed by the Sponsor, the blind should be broken by Parexel Pharmacovigilance team on behalf of the Sponsor (after Sponsor's approval) for that specific participant only (peek blind). The blind will be maintained for persons responsible for the ongoing conduct of the study (such as the study management, monitors and Investigators), and those responsible for data analysis and interpretation of results at the conclusion of the study such as biometric personnel. Unblinded information will only be accessible to those who need to be involved in the safety reporting to regulatory authorities and Independent Ethics Committees (IECs). Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

The IRT will be programmed with blind-breaking instructions. The assignment of study treatment may be unblinded in emergency situation when the knowledge of the study treatment assignment is considered absolutely necessary for the medical management of the participant or for clinical decision-making (i.e., when knowledge of the study treatment assignment would

impact a treatment decision, unblinding might not be required in many cases due to the biosimilarity and treatment options not being different between RGB-14-P and Prolia®). The Investigator has the sole responsibility for determining if unblinding of a participant's study treatment assignment is warranted. Participant safety must always be the first consideration in making such a decision. The Investigator should make an effort to contact the Parexel Medical Monitor, if possible, prior to unblinding. The applicable Parexel standard operating procedure (SOP) will be followed for blind-breaking procedures. In case of unblinding for safety reporting reasons, Parexel Pharmacovigilance reporting team has an IRT system access to obtain the treatment for a specific participant. In case of a medical emergency healthcare professionals should contact the Investigator. If the Investigator is not available, non-study healthcare professional may contact the emergency call centre for urgent information about the study drug and may break the blind if necessary (see Section 8.1.2). The treatment code may only be broken in case of emergency when knowledge of the treatment received is necessary for the proper medical management of the participant.

When a participant's study treatment assignment is unblinded, a comprehensive source note must be completed by unblinding the Investigator that includes the date and time, the name of the study personnel responsible and the reason(s) the participant's treatment code was unblinded. The source note must also include a record of the discussion with the Medical Monitor. All unblinding information is captured by the unblinded safety team in the safety database. The safety processing team who manages SAEs as well as the SAE Reporting Form remains blinded.

In all unblinding cases, Parexel should contact the Sponsor as soon as possible. In addition, the Clinical Research Associate, Clinical Operational Lead and the Project Lead should be informed. Following emergency unblinding, the participant's further participation such as safety follow-up examinations in the study should be discussed with the Sponsor by Parexel.

In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomisation/administration has been done accurately.

Further details regarding blinding, unblinding and communication routes can be found in the Blinding Management Plan.

6.4 Investigational Medicinal Product Compliance

At the investigational sites, in order to strictly maintain the blinded design of the study, nobody, except the delegated unblinded pharmacy staff, unblinded healthcare professional responsible for IMP administration or unblinded monitor should be in contact with the IMP, that keeps the

blinded design of the study intact. When participants are dosed at the site, they will receive study intervention under supervision from the Investigator or designee, under medical supervision. The date and time of each dose administered at the chosen site of administration (e.g., abdomen, thigh, upper arm, etc.) will be recorded in the source documents and recorded in the eCRF. The dose of IMP and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the IMP.

At the investigational site, all activities related to the handling of IMP until administration to a participant should be performed by the pharmacy staff/authorised designee. Unblinded site staff must not perform any clinical assessment. This person should be assigned by the Investigator and be responsible for:

- Receipt of IMP.
- Preparation of IMP for administration.
- Storage of IMP.
- Dispensing of IMP.
- Accountability and reconciliation of IMP.
- Preparation of IMP for destruction (used, expired, not fit to use, unused after last participant last visit).

For medical device events procedures see Section 6.1.2.

6.5 Prior and Concomitant Therapy

Medications are classified as prior if the administration stop date was before the first dose of IMP and as concomitant if ongoing or if started after IMP dosing.

The use of medications listed in exclusion criteria 20, 21 and 22 (Section 5.2) should be sought without time frame restrictions.

All restrictions on medications as listed in Section 6.5.1 are applicable for the entire duration of the study. Other concomitant medications that the participant receives on a regular basis may continue, if in the opinion of the Investigator, it does not put the participant at undue risk or does not interfere with the study evaluations. Concomitant medication use may be warranted for the treatment of AEs. All concomitant medications necessary for the health and well-being of a participant will be permitted. Any medication or vaccine (including over-the-counter or

prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- Brand name and generic/international non-proprietary names (INN) name.
- Route of administration.
- Reason for medication (e.g., AE, medical history, prophylaxis).
- Indication.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

Any changes in the dosage or regimen of a concomitant medication will be recorded.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Prohibited Therapy

The medications and interventions which are listed below will be prohibited during the study period unless required for AE/SAE management. If any of these prohibited therapies are applied the Medical Monitor should be contacted to discuss whether the participant may continue the study.

Participants must abstain from the use of the following concomitant treatment:

- 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 etelcacetide).

- Systemic glucocorticosteroids (≥ 5 mg prednisone or equivalent per day for ≥ 10 days or a total cumulative dose of ≥ 50 mg). Topical and inhaled glucocorticosteroids are allowed.
- Other bone active drugs including heparin (also low molecular weight heparins), vitamin K (supplementation or therapeutic dose), vitamin K antagonists (e.g., warfarin, acenocumarol), emtricitabine, tenofovir, adefovir, anti-convulsants (with the exception of benzodiazepines, gabapentin and pregabalin), systemic ketoconazole, ACTH, lithium, protease inhibitors, GnRH agonists, anabolic steroids.
- Invasive dental procedures (e.g., dental implants or oral surgery) and major surgeries or bone surgeries (unless required for AE/SAE management after careful consideration) will be prohibited during the study period.

See Section 5.2 for specific restrictions on prohibited medications.

6.5.2 Additional Study Treatments

According to the Prolia® USPI [3] and as indicated in the IB [1], as precautionary measure for denosumab use, all participants should have an adequate intake of calcium and vitamin D. Therefore, at latest from the first day of IMP dosing until the End-of-Study/Early Termination Visit all participants must take at least 1000 mg of calcium and at least 800 IU of vitamin D or calcitriol daily. Once weekly or monthly administration of higher vitamin D dose is allowed if this is the local practice and preference, but the average daily 800 IU should be achieved. Higher starting and maintenance doses of vitamin D and calcium supplementation are also permitted, especially for participants with serum vitamin D level in the lower range. Elemental calcium should be taken into consideration for calculation of the calcium dosage. Calcium and vitamin D will be provided locally by the study site.

Compliance with daily calcium and vitamin D intake will be monitored and assessed throughout the study.

If hypercalcaemia or hypocalcaemia occurs, the Investigator can modify the dietary intake of calcium and adjust the calcium and/or vitamin D dosage if needed, according to local practice. The change should be reported in the eCRF and hypercalcaemia or hypocalcaemia should be reported as an AE if clinically significant.

Intolerance to non-IMP may occur, especially for calcium. Calcium intolerance can manifest as bloating or constipation. The formulation and/or dose frequency (e.g., dose divided twice daily) can be changed to reduce intolerance and increase compliance at the Investigator's discretion. If intolerance continues after lowering the dose, temporary discontinuation may be considered.

Permanent discontinuation of calcium and/or vitamin D should be discussed with the Medical Monitor in the CRO and should be documented in the source data.

6.6 Dose Modification

Not applicable.

6.7 Intervention After the End of the Study

Discontinuation of treatment with denosumab has been associated with a rebound increase in bone turnover accompanied by rapid bone loss and subsequent increase in the risk of fractures, including multiple vertebral fractures, therefore administration of denosumab should not be delayed or stopped without transitioning the participant to another antiresorptive agent (e.g., bisphosphonates, hormone replacement therapy or SERMs) or in some cases other therapy may also be considered [15]. Consequently, the Investigator must ensure that in line with the local guidelines appropriate follow-up osteoporosis treatment is prescribed to all participants upon conclusion of the therapy with the study drug either due to early termination or upon completion of the study at 12 or 18 months. The subsequent treatment options will be discussed with the participant either at the Early Termination Visit or at the End-of-Study Visit and should be clearly documented in the source data.

7 Discontinuation of Investigational Medicinal Product and Participant Discontinuation/Withdrawal from the Study

7.1 Discontinuation of Investigational Medicinal Product, Participant Discontinuation/Withdrawal from the Study

It may be necessary for a participant to discontinue IMP. If IMP is discontinued, the participant may remain in the study to be evaluated, unless the participant withdraws consent, or it is against the participant's best medical interest or does not serve the well-being of the participant as deemed by the Investigator or Sponsor.

Participants will discontinue IMP if any of the following events occurs:

- Adverse drug reactions of grade 3 or 4 severity including but not limited to:
  - Drug-related hypersensitivity, anaphylactic reaction
  - Osteonecrosis of the jaw, osteonecrosis of the external auditory canal
  - Atypical femoral fracture
- Any relevant AE or SAE, if the Sponsor or Investigator deems it as medical reason to warrant IMP discontinuation. The Investigator must notify the Medical Monitor immediately if a participant discontinued the IMP because of an AE/SAE.
- Participant is pregnant or breastfeeds, see Section 8.5.5.
- Unsatisfactory therapeutic effect of the IMPs or disease progression (e.g., decrease of BMD or new osteoporotic fracture) that requires change of osteoporosis treatment, agreed by the Investigator.
  If a participant experiences BMD reduction of ≥ 5% from baseline at the total hip, femoral neck and/or the lumbar spine at any time during the study, the Investigator is required to explore if factors other than postmenopausal osteoporosis, such as non-compliance with vitamin D/calcium supplementation or secondary causes of osteoporosis could contribute to the BMD decrease, discuss implications for individual fracture risk, alternative treatment options and options for continuing in the study with the participant, and to document that discussion. If a decision is made to begin alternative treatment, the IMP must be discontinued. Please refer to Section 6.7 for details on the transition to another osteoporosis treatment at the conclusion of IMP therapy.
- Prohibited concomitant medication, unless a written confirmation is provided by the Sponsor that the participant may continue taking the IMP.

- Following emergency unblinding.
- At the discretion of the Investigator or Sponsor any circumstances that could prevent the participant to comply with the protocol requirements and study objectives.
- Withdrawal of consent. A participant may withdraw from the study at any time at her own request without giving any reasons.

If discontinuation of IMP or withdrawal of consent occurs, the Investigator should make effort to understand the primary reason for the participant's premature discontinuation or withdrawal of consent and record this information.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, she may request destruction of any samples taken and not tested, and the Investigator must document this in the study site records.

Every case of early discontinuation from study treatment should be discussed with the Medical Monitor and all reasonable effort should be made to retain the participant until all remaining study procedures are completed, except IMP administration until Week 52. If the participant opts not to continue with the completion of all remaining study procedures until Week 52, all reasonable effort should be made to complete the End-of-Study/Early Termination procedures as shown in the SoA (Table 1-1 and Table 1-2). Refer to the SoA (Table 1-1 and Table 1-2) for assessments to be done at the time of study discontinuation or early withdrawal.

7.2 Loss of Participants to Follow-Up

A participant will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or

local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

Study procedures and their timing are summarised in the SoA (Table 1-1 and Table 1-2). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue IMP.

Adherence to the study design requirements, including those specified in the SoA (Table 1-1 and Table 1-2), is essential and required for study conduct. The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study-specific protocol deviations specifications document.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

A summary blood log including volume as well as instruction for all sample collection, processing, storage and shipment information will be available in the Laboratory Manual.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. In the case of repeated measurements, the new results and the reason for repeat must be documented in the eCRF. Investigators and site staff should make reasonable effort to understand the reason for missing data and document it in the source data and eCRF. This requirement will be part of the Investigators' training and site staff will be re-trained in case of noncompliance.

8.1 Administrative Procedures

8.1.1 Informed Consent

Informed consent must be documented according to Appendix 1 (Section 10.1.3).

8.1.2 Participant Identification and Visit Reminder Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The Investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention allocation/randomisation, site

personnel will add the intervention/randomisation number to the participant identification card. At each visit participants will be provided with a participant identification and visit reminder card. The Investigator must update the visit reminder card at each visit with the details for the next visit.

The participant identification card also contains contact information for the emergency unblinding call centre so that a healthcare provider can obtain information about IMP in emergency situations where the Investigator is not available.

8.2 Screening and Eligibility Assessments

8.2.1 Eligibility Criteria

All inclusion and exclusion criteria will be reviewed by the Investigator or designee to ensure that the participant qualifies for the study.

The Investigator or designee must enter all screening data in the electronic data capture (EDC) system in a timely manner to allow the Parexel Medical Monitor to review eligibility data before participant is randomised. Only after Medical Monitor approval (i.e., there is no objection against inclusion of the participant), the Investigator or his/her delegate may contact the IRT.

8.2.2 Demography

Demographic data will be collected including age, gender, race and ethnicity as allowed by the local regulations.

8.2.3 Medical and Surgical History

Medical history and surgical history will be obtained by the Investigator or qualified designee. The medical history will collect all active conditions and any prior condition. The medical history will also include fracture history and active healing fracture assessment by Investigators. The medical history will be documented in the source documents and eCRF.

8.2.4 Prior and Concomitant Medications Review

The Investigator or qualified designee will review prior medication use in order to verify that the eligibility criteria are met and record those medications, including bone-specific medications, taken by the participant prior to the Screening Period.

Medications are classified as prior if the administration stop date was before the first dose of IMP and as concomitant if ongoing or if started after IMP dosing. The use of medications listed in exclusion criteria 20, 21 and 22 (Section 5.2) should be sought without time frame restrictions.

The Investigator or qualified designee will record concomitant medication, if any, taken by the participant during the study until the End-of-Study/Early Termination Visit (or longer if related to an SAE).

8.2.5 Screening Assessment

Participants who have signed the informed consent will undergo the following procedures and assessments:

- Height, without shoes (cm).
- Body weight, without shoes (kg).
- Body mass index (kg/m^2) to be calculated.
- History and current use of alcohol and/or drugs and tobacco products.
- Medical and surgical history.
- Physical examination (including oral cavity and dental health).
- Examine for any signs and/or symptoms of any acute or chronic infections including COVID-19.
- Vital signs.
- 12-lead ECG.
- Clinical laboratory tests including haematology, clinical chemistry, urinalysis and viral serology.
- Prior medication.
- Medical occurrence (AEs), if any, since the time of signing the ICF.
- Review of inclusion and exclusion criteria.
- Review of lifestyle restrictions.
- Dual energy X-ray absorptiometry assessment (see Section 8.3.1).
- Lateral spine X-ray (see Section 8.3.2).

The Screening visit may be conducted over the Screening period (i.e., more than 1 day can be utilised for Screening during the Screening period), if necessary, for logistical reasons.

8.2.6 Recommended Order of Assessments

The following recommended order will be in effect when more than one assessment is required at time point, please also see to the SoA (Table 1-1 and Table 1-2):

- 12-lead ECG.
- Vital signs:
  - Blood pressure.
  - Body temperature.
- Blood sampling for sCTX/P1NP.
- Blood sampling for immunogenicity and serum drug concentration assessment.
- Blood sampling for safety assessment.
- Urinalysis.
- Physical examination and other assessment.

8.3 Efficacy Assessments

8.3.1 Dual Energy X-ray Absorptiometry Measurement

Dual energy X-ray absorptiometry measurements will be used to confirm participant eligibility and to determine the change in BMD as indicated in the SoA (Table 1-1 and Table 1-2). If the participant withdraws from the study early a measurement during the Early Termination Visit will not be required if the previous measurement was taken within 5 weeks prior.

For all participants bone density will be measured at the lumbar spine, total hip and femoral neck. The lumbar spine scan must include L1 through L4 vertebrae. To be eligible for participation in the study, a participant must have a BMD consistent with a T-score $\leq$ -2.5 and $\geq$ -4.0 at the lumbar spine and at least 2 evaluable lumbar vertebrae during the Screening Period as confirmed by central independent review. For total hip and proximal femur, the left side should be used for all DXA scans at all study visits. If the right side must be used (e.g., due to implants) or is inadvertently used at Baseline, then it must be consistently used throughout the study.

The same DXA scanner should be used for all study procedures for a particular participant at each site. All DXA scans must be submitted to and analysed centrally by Parexel.

Detailed instructions on DXA scan acquisition can be found in the separate Image Acquisition Guideline.

8.3.2 Lateral Spine X-ray

Lateral spine X-ray assessment will be used to confirm participant eligibility and to determine the change in bone imaging/occurrence of fractures from Baseline as indicated in the SoA (Table 1-1 and Table 1-2). Semi-quantitative assessment using Genant scoring method of 0 – 3 for presence and severity of vertebral fractures (0 = normal, 1 = mild, 2 = moderate, 3 = severe) will be used [16]. The responsibility of other (e.g., incidental findings) analyses of the lateral spine X-ray, which are out of the scope of the central assessment (i.e., vertebral fracture assessment with Genant scoring method), remains with the Investigator. If the participant withdraws from the study early an image during the Early Termination Visit will not be required if the previous image was taken within 5 weeks prior. All X-rays must be submitted to and analysed centrally by Parexel.

Detailed instructions on lateral spine X-ray can be found in the Image Acquisition Guideline.

8.3.3 Fracture Assessment

Fracture rates (the incidence of vertebral and non-vertebral fragility fractures) will be monitored and assessed as a secondary efficacy endpoint throughout the study. In addition, any fracture (symptomatic and asymptomatic) that occurs during the study will be recorded as an AE (see Section 8.4). Fragility fractures are fractures that occur as a result of "low energy trauma", often from a fall from standing height or less, that would not normally result in a fracture.

8.3.3.1 Vertebral Fracture

Information on vertebral fractures will be centrally evaluated through the lateral thoraco-lumbar spine X-ray (see Section 8.3.2) scheduled as indicated in the SoA (Table 1-1 and Table 1-2). For central assessment of vertebral fractures by lateral spine X-ray, a visual semiquantitative grading scale will be used [16] and further defined in the Independent Review Charter. Details on the X-rays acquisition requirements are provided in the Image Acquisition Guideline.

8.3.3.2 Non-vertebral Fracture

The diagnosis of non-vertebral fractures will not require central X-ray reading and will be based on local radiological reports.

8.4 Safety Assessments

Safety assessment will consist of the regular monitoring of haematology, clinical chemistry, urinalysis, ECG, regular measurements of vital signs, physical examinations, injection site reactions and fracture assessment (see Section 8.3.3) as well as monitoring and recording of all AEs and SAEs. Any fracture (symptomatic and asymptomatic) that occurs during the study will be recorded as an AE. Consequently, any new or worsening fracture reported after central reading of lateral spine X-ray should be documented as an AE by the Investigator. Severity of vertebral fractures will be defined and reported using the Genant score (i.e., 1 = mild, 2 = moderate, 3 = severe). Planned time points for all safety assessments are provided in the SoA (Table 1-1 and Table 1-2).

8.4.1 Physical Examinations

A comprehensive physical examination will be performed as outlined in the SoA (Table 1-1 and Table 1-2) and will include assessments of general appearance and review of systems (head, eyes, ears, nose, mouth/oral cavity/throat/neck, thyroid, lymph nodes, dermatologic, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurological systems).

At all other visits physical examination might be performed as per the Investigator's discretion.

Height and weight will also be measured and recorded and body mass index (BMI) will be calculated. Height will be measured without shoes at the Screening Period and at all timepoints when BMI is measured. Weight will be measured as outlined in the SoA (Table 1-1 and Table 1-2) in light clothes and without shoes.

8.4.2 Vital Signs

Body (axillary, forehead or tympanic) temperature will be measured, pulse and blood pressure will be assessed as outlined in the SoA (Table 1-1 and Table 1-2). Respiratory rate to be assessed at the discretion of the Investigator.

Systolic and diastolic blood pressure and pulse measurements will be assessed after the participant has been sitting for at least 5 minutes with back supported and both feet on the floor, using a validated device. All blood pressure measurements should be performed on the same arm, as much as possible.

When timepoint for procedures overlap, it is recommended that vital signs are to be collected before blood sample collection.

8.4.3 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (Table 1-1 and Table 1-2) after 10 minutes rest in supine position using an ECG machine.

According to the Prolia® label, rarely, patients receiving Prolia® may develop hypocalcaemia, which may also lead to QT prolongation.

Safety ECGs will be reviewed and interpreted on-site by the Investigator. Abnormalities in an ECG will be assessed as "clinically significant" or "not clinically significant".

8.4.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Table 1-1 and Table 1-2) for the timing and frequency.

A central laboratory will be used to measure laboratory parameters that are to be listed in the clinical study report. All blood samples will be obtained by venepuncture.

Full instruction for collection, aliquoting, labelling, processing, storage and shipment of samples will be provided in the Laboratory Manual. The actual date and time (24-hour clock time) of blood sampling will be recorded. Any deviation in the storage conditions and sample processing defined in the Laboratory Manual should be reported to the central laboratory analysing the samples and to the Clinical Research Associate.

Sites will perform a urine dipstick (all dipstick results should be reported in the eCRF). In case of abnormal results, a urine sample may be sent to the central lab for full analysis if deemed necessary by the Investigator. See Appendix 2 (Section 10.2).

The Investigator will evaluate the clinical relevance of each laboratory value outside of the reference range. This evaluation will be based upon the nature and degree of the observed abnormality. Any abnormal clinical laboratory test result (haematology, clinical chemistry or urinalysis) that worsen from baseline and is considered to be clinically significant in the medical and scientific judgement of the Investigator are to be recorded as AEs or SAEs. Additionally, abnormal laboratory values that induce clinical signs or symptoms or that require therapy must also be recorded as AEs in the eCRF.

In case of an abnormal result, the Investigator may consider repeating the test once in order to rule out laboratory error. Unscheduled laboratory assessments may be obtained at any time during the study upon Investigator's discretion.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or AEs as appropriate.

8.4.4.1 Hypocalcaemia

Clinical monitoring of calcium level and vitamin D will be performed as indicated in the SoA (Table 1-1 and Table 1-2). Hypocalcaemia (albumin-adjusted serum calcium < 2.1 mmol/L [< 8.4 mg/dL]) must be corrected by adequate supplementation of calcium and vitamin D before initiating treatment and administration of IMP.

According to local guideline or practice and upon the discretion of the Investigator, (preferably albumin-adjusted) serum calcium level may be measured prior to the administration of IMP or at any timepoint at local laboratory. The results, as well as the lower and upper limit of normal value of (albumin-adjusted) serum calcium at the local laboratory should be documented in the eCRF. Clinically significant abnormal values should be reported as an AE. However, for clinical study report purposes the values from the central laboratory will be considered.

In the case of hypocalcaemia, the following procedures should be followed:

- Temporarily withhold IMP dosing.
- Upon Investigator's discretion, perform a physical examination or additional assessments, e.g., ECG.
- Administer additional calcium as per Investigator's discretion (see Section 6.5.2) as deemed acceptable as per local guidelines or practice.
- Repeat albumin-adjusted serum calcium test as many times as deemed appropriate, until hypocalcaemia resolves.
- Continue with study treatment only if hypocalcaemia is resolved and is not contraindicated any more.
- Contact the Medical Monitor if additional information is required.

8.4.5 Local Tolerance (Skin Examination)

A local tolerance (skin examination) assessment will be done by the Investigator as indicated in the SoA (Table 1-1 and Table 1-2). On dosing days, injections site reaction assessment should be done predose (i.e., for exclusion of a pre-existing, not IMP injection induced condition) and approximately 1 hour postdose, during this 1 hour period (i.e., from dosing to the injection site assessment) the participant will stay in the clinic for general safety observation. Any further assessment of the injection site or prolonged observation of the participant may be done at the

discretion of the Investigator. The grading of severity of each injection site reaction will be based on the Common Terminology Criteria for Adverse Events (CTCAE) v 5 criteria included in Table 8-1. Injection site reactions with a grading of ≥ 1 will be recorded as an AE.

Table 8-1 Common Terminology Criteria for Adverse Events Injection Site Reaction Grading

Grade	Reaction
Grade 1	Tenderness with or without associated symptoms (e.g. warmth, erythema, itching)
Grade 2	Pain, lipodystrophy, edema, phlebitis
Grade 3	Ulceration or necrosis, severe tissue damage, operative intervention indicated
Grade 4	Life-threatening consequences, urgent intervention indicated

Source: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

8.5 Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). The definitions of AEs and SAEs caused by device incident (Prolia®) or device deficiency (RGB-14-P) can be found in Appendix 3 (Section 10.3).

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative). Information on device incident/deficiency will be reported in the Product Complaint Form by unblinded site staff (see Section 6.1.2). Device incident or device deficiency that cause site staff related injury will be reported in the Product Complaint Form by unblinded site staff as it is described in the Addendum to Investigator Manual and the Product Complaint Procedure.

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AE, considered related to the IMP or the study, or that caused the participant to discontinue the IMP (see Section 7). In order to fulfil regulatory obligations, the Investigator is responsible for the documentation of any AEs or SAEs (whether or not caused by a device incident/deficiency) that occur during the study.

8.5.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and SAEs will be collected from the signing of ICF until the End-of-Study or Early Termination Visit at the time points specified in the SoA (Table 1-1 and Table 1-2) or anytime during the study.

All SAEs including, but not limited to SAEs caused by device incidents/deficiencies, will be recorded and reported to Parexel within 24 hours of it being available, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to Parexel within 24 hours of it being available.

In addition, all AEs caused by device incidents/deficiencies are to be reported as AEs following the same reporting periods and procedures as all study AEs. Further details regarding device incident or device deficiency AEs can be found in Appendix 3 (Section 10.3).

Any adverse effect on health or safety, any life-threatening problem or death caused by, or associated with the devices needs to be recorded in the eCRF and reported as it is defined in the SAE processing procedure, the Addendum to Investigator Manual and the Product Complaint Procedure.

Investigators are not obliged to actively seek AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the IMP or study participation, the Investigator must promptly notify the Sponsor.

8.5.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.5.3 Follow-up of Adverse Events and Serious Adverse Events

All participants with AE/SAEs that occur during the study will be treated according to daily clinical practice. After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AE/SAEs (caused by device incidents/deficiencies or not) will be followed until resolution (i.e., recovery or evident trend towards recovery, recovery with sequalae), stabilisation or until the condition determined to be chronic or permanent, or the participant is lost to follow-up (as defined in Section 7.2). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.5.4 Regulatory Reporting Requirements for Serious Adverse Event

Prompt notification (within 24 hours, see Appendix 3 [Section 10.3]) by the Investigator to Parexel of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of the IMP under clinical investigation are met.

The Sponsor (Parexel on behalf of the Sponsor) has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/IEC, and Investigators.

The Sponsor (Parexel on behalf of the Sponsor) has a legal responsibility to report, without delay to all Member States in which the clinical study is being conducted, including:

1. any SAE that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible,
2. any device event that might have led to an SAE, if appropriate action had not been taken, if intervention had not occurred, or circumstances had been less fortunate,
3. any new findings in relation to any event referred to in points 1 and 2 above.

For all studies including those which use combination products such as RGB-14-P and Prolia®, Investigator safety reports must be prepared for SUSAR according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

On behalf of the Sponsor, after Sponsor's approval, the Parexel Pharmacovigilance team shall report any SUSARs to the regulatory agencies and IECs, if applicable. The Parexel Pharmacovigilance team shall provide the Sponsor with local regulatory reporting requirements related to pharmacovigilance activities. The Parexel Pharmacovigilance team shall inform the Investigator in the clinical study about the occurrence of SUSARs.

In addition, on behalf of the Sponsor, after Sponsor's approval, the Parexel Pharmacovigilance team shall report any medical device incident or deficiency that qualifies for a reportable medical device event according to the above-mentioned criteria. The Parexel Pharmacovigilance team shall provide the Sponsor with local regulatory reporting requirement related to medical devices.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAE) from Parexel will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.5 Pregnancy

For postmenopausal participants, pregnancy is not expected. In the rare occurrence of pregnancy:

- Details of all pregnancies in female participants will be collected after signing of the ICF.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and IMP must be discontinued.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs.

As a general rule, the study medication must be discontinued, though the participant may stay in the study and follow the assessments, if she wishes to do so. Each pregnancy occurring after signing of the informed consent must be reported to Parexel within 24 hours of learning of its occurrence. Pregnancy should be recorded and reported by the Investigator to Parexel or its designated representative. The pregnancy should be followed up to determine the outcome, including spontaneous or voluntary termination, details of the birth and the presence or absence of any birth defects, congenital abnormalities or maternal and/or newborn complications. Generally, follow-up will not be required for longer than 8 weeks beyond the actual delivery date. Any termination of the pregnancy will be reported, regardless of foetal state (presence or absence of anomalies) or indication for the procedure.

Pregnancy should be recorded and reported by the Investigator to Parexel or its designated representative. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study medication and any pregnancy outcomes. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to IMP by the Investigator will be reported to the Sponsor or its designated representative. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.6 Treatment of Overdose

The Sponsor does not recommend specific treatment for an overdose. There is no experience with overdose in clinical studies with RGB-14-P. Denosumab has been administered in clinical studies using doses up to 180 mg every 4 weeks, with no additional adverse reactions observed. [1] As RGB-14-P and Prolia® are supplied in pre-filled syringes and participants will not self-administer the IMP, incidences of overdose are not expected.

Accidental or intentional overdose of the intended dose of study drug requires reporting to the Parexel Medical Monitor within 24 hours of learning.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities.
3. Document the quantity of the excess dose in the eCRF.

8.7 Immunogenicity Assessments

Antibodies to denosumab (anti-RGB-14-P antibodies and anti-Prolia® antibodies) will be evaluated in serum samples collected from all participants according to the SoA (Table 1-1 and Table 1-2). Blood samples will be collected for determination of binding anti-drug antibodies (ADAs) and neutralising antibodies (NAbs). Additionally, serum samples should also be collected at the final visit from participants who discontinued IMP or were withdrawn from the study. These samples will be tested by the Sponsor.

Full instruction for collection, aliquoting, labelling, processing, storage and shipment of samples will be provided in the Laboratory Manual. The actual date and time (24-hour clock time) of blood sampling will be recorded. Any deviation in the storage conditions and sample processing defined in the Laboratory Manual should be reported to the central laboratory and Sponsor's laboratory analysing the samples.

Serum immunogenicity samples will be assessed for ADAs according to the following stepwise analytical approach:

1. Screening analysis (assay).
2. For those who had a positive screening result, confirmatory analysis will be done.
3. Confirmed positive samples will be titrated.

4. Confirmed ADA positive samples will be analysed with neutralising assay to detect the neutralising potency of ADAs.

Serum samples will be screened for ADAs and the titre of confirmed positive samples will be reported. Confirmed ADA positive samples will also be analysed with neutralising assay to detect the neutralising potency of ADAs. Other analyses may be performed to verify the stability of ADAs.

The detection and characterisation of ADAs will be performed using validated assay methods by the Sponsor. In parallel, blood samples will be collected together with the immunogenicity samples for determination of denosumab serum concentration to enable interpretation of the antibody data (Section 8.8).

Samples may be stored for a maximum of 15 years following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to denosumab. Samples may also be used for validation of the analytical methods and generation of human positive control.

Participant confidentiality will be maintained.

8.8 Serum Drug Concentration

Blood samples will be collected at the time of immunogenicity sample collection for measurement of serum concentrations of denosumab (RGB-14-P and Prolia®) as specified in the SoA (Table 1-1 and Table 1-2), to support the interpretation of immunogenicity data. These samples will be tested by the Sponsor.

Full instruction for collection, aliquoting, labelling, processing, storage and shipment of samples will be provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded. Any deviation in the storage conditions and sample processing defined in the Laboratory Manual should be reported to the central laboratory and Sponsor's laboratory analysing the samples.

Samples collected for analyses of denosumab serum concentration may also be used to evaluate safety, efficacy or immunogenicity aspects that address concerns arising during or after the study. Serum denosumab concentration will be determined using a validated assay method by the Sponsor.

Samples may be stored for a maximum of 15 years following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis. Samples may also be used for validation of the analytical methods and generation of human positive control.

Participant confidentiality will be maintained.

8.9 Pharmacodynamics

In this study PD markers such as serum P1NP and CTX will be measured and compared as specified at the endpoints (Section 3).

Area under the effective curve (AUEC) after first dose until Day 183 percent change from Baseline (%CfB) in sCTX will be estimated as key PD parameter.

Blood samples will be collected for measurement of serum concentrations of sCTX and P1NP as specified in the SoA (Table 1-1 and Table 1-2).

Instructions for the collection and handling of biological samples will be provided by the bioanalytical laboratory. Full instructions for collection, aliquoting, labelling, processing, storage and shipment of samples will be provided in the Laboratory Manual. The actual date and time (24-hour clock time) of blood sampling will be recorded. Any deviation in the storage conditions and sample processing defined in the Laboratory Manual should be reported to the bioanalytical laboratory analysing the samples and to the Clinical Research Associate.

Samples collected for analyses of sCTX and P1NP serum concentration may also be used to evaluate safety or efficacy aspects that address concerns arising during or after the study.

Analysis will be performed in a blinded manner. Participant confidentiality will be maintained.

8.10 Genetics

Genetics are not evaluated in this study.

8.11 Biomarkers

Biomarkers are not evaluated in this study.

8.12 Medical Resource Utilisation and Health Economics

Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9 Statistical Considerations

9.1 Statistical Hypotheses

The null hypothesis being tested is the RGB-14-P and Prolia® are not equivalent in favour of the alternative hypothesis that the two treatments are equivalent.

- Efficacy estimand for EMA submission

CCI [redacted]

CCI [redacted]

Where:

μ_{RGB}: BMD mean %CfB in RGB-14-P study arm

μ_{Prolia}: BMD mean %CfB in Prolia® study arm

$\delta = \mu_{RGB\text{-}14\text{-}P} - \mu_{Prolia}$

Significance level = 0.05 (two-sided), i.e., 95% (two-sided) confidence interval (CI) to be contained within acceptance region.

- Efficacy estimand for FDA submission

Two separate hypothesis tests to be applied:

  - Non-superiority of RGB-14-P compared to Prolia®

    CCI [redacted]

    CCI [redacted]

    Significance level = 0.05 (one-sided)

  - Non-inferiority of RGB-14-P compared to Prolia®

    CCI [redacted]

    CCI [redacted]

    Significance level = 0.05 (one-sided)

- PD endpoint

Null Hypothesis H_0: Geometric Mean Ratio (GMR, RGB-14-P / Prolia®) not contained within [80.00%, 125.00%]

Alternative Hypothesis H_1: GMR (RGB-14-P / Prolia®) contained within [80.00%, 125.00%]

Significance level = 0.05 (two-sided), i.e., 95% (two-sided) CI to be used.

9.2 Sample Size Determination

Approximately 434 women with postmenopausal osteoporosis are 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 will be stratified by previous use of bisphosphonates and geographical region.

It is planned that 198 participants will continue to participate during the Transition Period, which should ensure to have 180 evaluable participants; approximately 66 participants will continue on the RGB-14-P arm, whereas approximately 132 participants initially assigned to the Prolia® arm will be re-randomised 1:1 whereby approximately 66 participants will continue to receive Prolia® and approximately 66 participants will be switched to RGB-14-P.

Based on a meta-analysis of 3 different studies conducted with denosumab [11, 12, 17], sample size was calculated from the following parameters:

- The primary parameter is the %CfB in lumbar spine BMD.
- CCI [redacted]
  CCI [redacted]
- 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); such a difference between study arms is supposed to be common across study strata.
- The expected (true) common standard deviation is 3.44.

CCI [redacted]
CCI [redacted]

With regards to the PD co-primary endpoint, healthy volunteer data [18] was used for the sample size calculations due to the lack of information on AUEC $sCTX_{0\text{-}m6}$ derived from the participants

population. The expected variability to the proposed PD endpoint is considered to be significantly lower than that of the proposed efficacy endpoint (in study NCT2053753 the interCV of AUEC $sCTX_{0\text{-}m6}$ was approximately 28%). Therefore, no formal sample size calculation was performed for AUEC $sCTX_{0\text{-}m6}$.

Calculating with a dropout rate of 1/6, 217 participants per arm are 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 $2 \times 217 = 434$ participants are evaluable, the power will stay below 95%.

A subset of approximately 66 participants from the RGB-14-P arm and approximately 132 participants from the Prolia® arm (approximately 198 participants in total) will participate in the Transition Period, which should ensure to have 60 evaluable participants per arm:

- Approximately 66 participants who received RGB-14-P in the Main Period will continue with RGB-14-P in the Transition Period;
- Approximately 66 participants who received Prolia® in the Main Period will switch to RGB-14-P in the Transition Period;
- Approximately 66 participants who received Prolia® in the Main Period will continue with Prolia® in the Transition Period.

Sample size selection for the Transition Period is not driven by statistical assumptions for formal hypothesis testing but was based on the safety objective for this study period. The table below (Table 9-1) provides the probability for a sample size (N) of 60 and 66 evaluable participants to observe at least 1 participant per AE, considering different frequencies of AE.

Table 9-1 Probability to Observe at Least One Participant with a Given Adverse Event

Frequency of AE	Probability to observe at least one participant with a given AE	
	N = 60	N = 66
5%	95.39%	96.61%
10%	99.82%	99.90%
15%	99.99%	100.00%
20%	100.00%	100.00%
25%	100.00%	100.00%

AE = adverse event

With 60 participants, events which occur at a frequency of 10% or more will be detected with at least 99% probability, while events which occur at a frequency of 5% or more will be detected with at least 95% probability. It is understood that slightly increasing the number of evaluable participants in a range from 60 to 66, the probability of detecting events will slightly increase accordingly.

9.3 Populations for Analyses

For purposes of analysis, the following analysis sets are defined:

Table 9-2 Populations for Analysis

Population (Analysis Set)	Description
ENR	All participants who signed the informed consent form (including screening failures).
FAS	The FAS comprises all participants to whom the IMP has been randomised.
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.
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. A precise definition of "as actually received" will be added in the SAP.
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 measurements.
IAS	The IAS consists of all participants in the safety population who have at least one available immunogenicity assessment and do not have any protocol deviations that have a relevant impact on immunogenicity evaluations.

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; P1NP = 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

The roles of the Full Analysis Set (FAS) and Per Protocol Set (PPS) will be detailed in Section 9.4.

9.4 Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalised prior to Database Lock and unblinding. Below is a description of planned statistical analyses. Further details are presented in the SAP.

9.4.1 General Considerations

Continuous data will be summarised by treatment group using descriptive statistics (number, mean, median, standard deviation [SD], minimum and maximum). Categorical data will be summarised by treatment group using frequency tables (frequency and percent).

Unless otherwise specified, baseline will be taken as the last available assessment prior to randomisation. Repeated and unscheduled assessments will be included in listing. Except considered as baseline, the repeated and unscheduled assessments will not be included in the summaries (if the repeat was necessitated by a technical issue/e.g., incorrect sampling processing/i.e., there is not a result or the result is not valid because of the technical issue, the repeat value will be considered and included in the summaries).

Similarity between RGB-14-P and Prolia® will be assessed based on the simultaneous success of hypothesis tests for all primary endpoints. Alpha adjustment is not planned.

Statistical tests will be two-sided and will be performed at the 5% level of significance, thus 95% CIs will be computed, unless otherwise stated.

9.4.2 Estimands

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. From this end, efficacy analysis will be defined with terms used for the estimand concept.

Table 9-3 Summary of the primary and secondary estimands

Estimands	**Primary: "Treatment Policy" estimand (TP)**	**Secondary: "Principal Stratum" estimand (PS)**
Clinical Question of Interest	Do RGB-14-P and US licensed Prolia® have a similar efficacy and a similar effect on BMD at the lumbar spine at Week 52 in females with postmenopausal osteoporosis regardless of the ICEs occurring during the Double-Blind phase?	Do RGB-14-P and US licensed Prolia® have a similar efficacy and a similar effect on BMD at the lumbar spine at Week 52 in females with postmenopausal osteoporosis in the Principal Stratum of participants who would not experience any ICEs on either treatment arms?
Variable	Percent increase in BMD from Baseline to Week 52, i.e., %CfB, is the primary study endpoint and is defined as: %CfB = (Post Baseline – Baseline) / Baseline * 100	
ICE	ICE1: The first and/or the second dose of randomised IMP is not administered ICE2: The participants received other medication alongside the IMP, which affects the primary variable (please refer to Section 6.5.1 [Prohibited Therapy])	
ICE Strategy	ICE1: Treatment policy strategy will be applied; All follow-up is relevant to the	Principal stratum casual estimand strategy will be used: Only participants who would

Estimands	**Primary: "Treatment Policy" estimand (TP)**	**Secondary: "Principal Stratum" estimand (PS)**
	clinical question, in line with the ITT-principle. ICE2: 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.	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.
Treatments	Test product: RGB-14-P subcutaneous injection 60 mg Reference product: Prolia® subcutaneous injection 60 mg	
Study Population as defined in Section 5	Females with postmenopausal osteoporosis	The principal stratum of females with postmenopausal osteoporosis who would not experience any ICEs on either treatment
Population-level Summary	Difference of means between the test and reference arms in change from baseline BMD: $\delta = \mu_{RGB\text{-}14\text{-}P} - \mu_{Prolia}$ μ_{RGB}: BMD mean %CfB in RGB-14-P study arm μ_{Prolia}: BMD mean %CfB in Prolia® study arm	
Analysed data points	All captured data points in the FAS are included to the analysis.	All captured data points in the PPS are included to the analysis.
Main Estimator	For EMA submission: δ will be estimated by using ANCOVA model (SAS PROC GLM) with the following factors: • Randomised treatment • Baseline BMD value • Previous use of bisphosphonates • Geographical region • Machine type • Machine type * Baseline BMD value interaction Missing data will be assumed to be MCAR and will not be imputed (see Section 9.4.5)	δ will be estimated by using ANCOVA model (SAS PROC GLM) with the following factors: • Treatment • Baseline BMD value • Previous use of bisphosphonates • Geographical region • Machine type • Machine type * Baseline BMD value interaction In the event of missing primary endpoint, to help alleviate the concern on the uncertainty introduced by missing data with potential impact on the integrity of randomisation, the strategy analysis with MI will be followed (as described Section 9.4.5)
	For US FDA submission: δ will be estimated by using ANCOVA model (SAS PROC GLM) with the following factors: • Treatment • Baseline BMD value • Previous use of bisphosphonates • Geographical region • Machine type • Machine type * Baseline BMD value interaction In the event of missing primary endpoint, to help alleviate the concern on the uncertainty introduced by missing	

Estimands	Primary: "Treatment Policy" estimand (TP)	Secondary: "Principal Stratum" estimand (PS)
	data with potential impact on the integrity of randomisation, the strategy analysis with MI will be followed (as described in Section 9.4.5)	
Sensitivity Estimator	For EMA submission: As a sensitivity estimation for the primary analysis of the primary endpoint, missing data may be imputed using MI rules. Criteria will be specified in the SAP, techniques proposed by Jakobsen et al, 2017 will be considered [19]. In case MCAR assumption appears to be questionable due to high amount or imbalanced distribution of missing data, relevance of the Sensitivity Estimator may increase. For FDA submission: Robustness of the main estimator will be assessed by using two-dimensional tipping point analyses allowing assumptions about missing outcomes in the two treatment arms to vary independently, including scenarios where the difference between imputed test and reference values is assumed to be beyond the predefined equivalence margin. Details will be provided in the SAP.	Due to the parallel design, robustness of the estimator will be assessed by tipping point analysis [20].

ANCOVA = analysis of covariance; BMD = bone mineral density; %CfB = percentage change from baseline; EMA = European Medicines Agency; FAS = Full Analysis Set; FDA = Food and Drug Administration; ICE = intercurrent event; MCAR = missing completely at random; MI = multiple imputation; MNAR = missing non at random; PPS = Per Protocol Analysis Set; SAP = Statistical Analysis Plan; US = United States

Descriptive analysis of the number, proportion, reasons and timing of intercurrent events (ICEs) will be presented.

9.4.2.1 Supplementary (tertiary) estimand

The supplementary estimand of BMD %CfB at Week 52 will utilize 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 set. The same ICEs will be applied as for the primary and secondary estimands.

Primary endpoint will be analysed by using mixed model for repeated measures (MMRM) with the following factors:

- Randomised treatment
- Baseline BMD value
- Previous use of bisphosphonates
- Geographical region
- Machine type
- Machine type * Baseline BMD value interaction
- Study Week
- Study Week * Treatment interaction

Missing data will be assumed to be missing completely at random (MCAR) and will not be imputed.

9.4.3 Primary pharmacodynamic analysis

The individual serum concentration of sCTX and P1NP will be listed and summarised by treatment group at each planned sampling time using descriptive statistics. Percent change from baseline (%CfB) will be derived from sCTX concentrations (100 * (postdose sCTX – baseline sCTX) / baseline sCTX), listed and summarised in tabular and graphical format. Percent change from baseline (%CfB) of P1NP will be calculated in a similar manner.

To evaluate the AUEC $sCTX_{0\text{-}m6}$ (required as primary endpoint for EMA and secondary for FDA), the treatment comparison will be made using the analysis of variance (ANOVA) on log-transformed data. Pharmacodynamic equivalence will be assessed if the 95% CI of the treatment ratio is contained within the acceptance limits of 80% to 125%.

9.4.4 Additional analyses

9.4.4.1 Efficacy

Below secondary endpoints will be analysed descriptively:

- Percent change from Baseline in total hip BMD at Weeks 26, 52 and 78.
- Percent change from Baseline in lumbar spine BMD at Weeks 26 and 78.
- Percent change from Baseline 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.

9.4.4.2 Pharmacodynamics

Below secondary endpoints will be analysed descriptively:

- Percent change from Baseline in serum P1NP at Weeks 4, 26, 52 and 78.
- Percent change from Baseline in sCTX at Weeks 4, 26, 52 and 78.

9.4.4.3 Safety

All safety analyses will be performed on the Safety Analysis Set.

Safety information will be summarised with descriptive statistics when appropriate. Tabulations will be provided for categorical data.

Safety analyses will be conducted "as treated".

9.4.4.3.1 Adverse Events

Assessment of safety will be done by determining the number of participants with any AE, including SAE.

Reported AE terms will be mapped to current version of Medical Dictionary for Regulatory Activities (MedDRA)-preferred terminology. All reported events will appear in AE listings; however, only treatment-emergent adverse events (TEAEs) will be summarised. A TEAE is an AE that starts or increases in severity on or after the first administration of study treatment up to the End-of-Study/Early Termination Visit following the last administration of study treatment.

Safety population data sets will be used for safety analysis:

- Adverse events will be coded according to MedDRA.
- The occurrence of AEs or adverse reactions, SAEs or serious adverse reactions and AEs or adverse reactions resulting in withdrawal will be summarised and analysed in the form of a frequency table (number of cases, number of participants with cases and incidence).
- The occurrence of varying severity orders of AEs or adverse reactions, SAEs or serious adverse reactions and AEs or adverse reactions resulting in withdrawal will be subject to descriptive statistical analysis in the form of a frequency table (number of cases, case and incidence) according to system organ class and preferred term.
- A detailed list of various AEs or adverse reactions, SAEs or serious adverse reactions and AEs or adverse reactions resulting in withdrawal will be created.

- Listing for any device incident or device deficiency AE or SAE will be created, including but not limited to seriousness, outcome and action taken.

9.4.4.3.2 Other Safety Data

Other safety parameters (e.g., laboratory test values, ECGs, vital signs and injection site assessment) will be summarised using descriptive statistics such as mean, standard deviation, minimum and maximum values.

Safety Analysis Set will be used for safety analysis:

- Changes in the clinical significance determination of laboratory indicators, ECG, physical examinations and local tolerance at each visit after administration and baseline test results will be described in the form of shift tables.
- The laboratory indices and vital signs examinations will be subject to descriptive statistical analysis according to treatment arm and visit as well as changes from baseline.
- A detailed list of laboratory indices, ECG, vital signs, clinically significant physical abnormalities and local tolerance will be created.
- Number and intensity of injection site reaction.
- Fracture assessment (details on analysis will be further described in the SAP).

9.4.4.4 Immunogenicity

All immunogenicity results (ADA confirmed positive or negative, ADA titres and neutralising activity) will be listed and summarised by treatment group, assay type and sampling point. The incidence of participants who develop binding ADAs and NAbs will be compared by visit and overall descriptively. More details will be provided in the SAP.

9.4.5 Handling of Missing Data

In general, if not stated otherwise, missing data will not be imputed.

Missing BMD baseline values would lead to impossibility to include the participant in the statistical analysis of the primary and secondary estimand, but due to eligibility review performed by the Medical Monitor, the probability of this phenomenon is negligeable.

Missing data in case of the analysis of the efficacy estimands (see Section 9.4.2) will be handled as follow:

- For EMA submission, missing data will be assumed to be MCAR and will not be imputed.

- For FDA submission, two separate one-sided tests, i.e., a test of non-inferiority and a test of non-superiority, will be conducted with each alpha = 0.05 and with missing data imputed under the corresponding null using a multiple imputation (MI) method. Specifically, for the first test, i.e., test of non-inferiority, missing values for the RGB-14-P group will be imputed under the corresponding CCI [redacted]; for the second test, i.e., test of non-superiority, missing values for the RGB-14-P group will be imputed under the corresponding CCI [redacted]. Overall, RGB-14-P will be claimed to be equivalent to Prolia® in the event that both $H_{0(\text{non-inf test})}$ and $H_{0(\text{non-sup test})}$ are rejected; considering the use of MI, all randomized subjects will be included in the analysis. In addition, a sensitivity tipping point analysis will be conducted to assess the robustness of the results, at both week 52 and week 78. Details will be provided in the SAP.

In the primary PD analysis participants with missing sCTX sampling at Baseline will not be included in the analysis of the AUEC $sCTX_{0\text{-}m6}$, additionally to be included in the analysis of the AUEC $sCTX_{0\text{-}m6}$, participants will need to have at least 6 postbaseline available results of which:

- Results within Week 1, Week 2 and Week 4.
- At least one available result within Week 8 and Week 12.
- At least one available result within Week 17 and Week 21
- Results within Week 26.

Participants with missing results from two consecutive timepoints will not be eligible for analysis.

Serum CTX concentration below the limit of quantification (BLQ) will be considered as BLQ in summary tables and graphically representation, including derivation of AUEC.

9.4.6 Other Analyses

9.4.6.1 Disposition of Participants

Participants entering and completing the study will be listed and summarised using number and percentage.

Participants excluded from each analysis sets will be listed including the reason for exclusion. Participants disposition will be summarised and will include the following information: number of participants randomised and dosed, number and percentage of participants completing the study and the number and percentage of participants who were withdrawn (including reasons for withdrawal). Participants disposition will be summarised.

Participants discontinuations will be listed including the date of study exit, duration of treatment (i.e., number of IMP doses received) and reason for discontinuation. A listing of informed consent response will also be presented.

A randomisation listing will be presented which includes but is not limited to the following: each participant's randomisation number, the participant's full enrolment number, the treatment to which the participant has been randomised and the location of the clinical unit.

9.4.6.2 Protocol Deviations

Protocol deviations will be listed by participant, reasons and timing of the deviation. Major protocol deviations which are considered to impact efficacy analyses will be identified prior to unblinding and may lead to exclusion of participants from the PPS analysis set.

9.4.6.3 Demographics and Baseline Characteristics

Demographic and anthropometric variables (age, sex, ethnicity, race, height, weight, and BMI) will be listed by participant. Demographic characteristics (age, sex, ethnicity, and race) and anthropometric characteristics (height, weight, and BMI) will be summarised descriptively by calculating means, medians, quartiles minimum and maximum for continuous variable, and frequencies and percentages for categorical variables. The denominator for percentages will be the number of participants in the safety population for each treatment arm or for all participant as applicable.

Medical history data will be listed by participant including visit, description of the disease/procedure, MedDRA system organ class, MedDRA preferred term, start date and stop date (or ongoing if applicable).

9.4.6.4 Prior and Concomitant Medication

Prior medications are those that started and stopped prior to the first dose of IMP. Concomitant medications are those taken after dosing (including medications that started prior to dosing and continued after).

Prior and concomitant medications will be listed by participant and will include the following information: brand name and generic/INN name, preferred term, the route of administration, dose, frequency, start date/time, stop date/time and indication.

Prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary latest version.

9.4.6.5 Investigational Medicinal Product Administration

A listing of IMP administration will be created and will include the date, time and site of administration.

9.5 Interim Analyses

No interim analysis will take place.

9.6 Data Monitoring Committee

Not applicable.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
  - Applicable ICH Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
  - Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulation (CFR), ICH GCP guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the participant or her legally authorised representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date and time the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most recent version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

Participants who are rescreened are required to sign a new ICF.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all participants subsequently enrolled in the study as well as those currently enrolled in the study.

10.1.4 Data Protection

Parexel and the Sponsor will take appropriate measures to ensure the processing of personal data and the free movement of such data are handled according to the EU General Data Protection Regulation 2016/679.

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, IBs and other material) will be stored appropriately to ensure their confidentiality. The Investigator and members of his/her research team (including the IEC) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from participants who wish to participate in the study or to comply with regulatory requirements.

Participants will be assigned unique identifiers (enrolment and randomisation number) by Parexel. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Study Data

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, IBs and other material) will be stored appropriately to ensure their confidentiality. The Investigator and members of his/her research team (including the IEC) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from participants who wish to participate in the study or to comply with regulatory requirements.

The anonymity of participants must be maintained. Participants will be specified on study documents by their enrolment/randomisation number, initial or birth year, not by name. Documents that identify the participant (e.g., the signed ICF) must be maintained in confidence by the Investigator.

The clinical study may be considered for publication in the scientific literature irrespective of whether the results of the clinical study are positive or negative (Appendix 1 [Section 10.1.9]). In addition, the results of clinical studies will be provided on the publicly funded websites such as www.ClinicalTrials.gov, www.clinicaltrialsregister.eu, in line with the applicable regulations.

10.1.6 Data Quality Assurance

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategies (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- Parexel is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- All data generated by the site personnel will be captured electronically at each study centre using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data centre, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

- If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the Clinical Research Associate will freeze the eCRF page.
- The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.
- After database lock, the Investigator will receive copies of their participant data for archiving at the investigational site. The data will also be extracted and provided to the Sponsor.
- Monitoring visits at site might be limited to a minimum required as deemed appropriate during the COVID-19 pandemic.

10.1.7 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents (including X-ray and DXA films/images) are filed at the Investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The study may be halted for evaluation of possible risk to participants, prior to decision as to whether to terminate the study if any of the following criteria are met:

- The occurrence of an SAE, if considered to be at least possibly related to the IMP.
- The occurrence of 2 severe or clinically significant AEs, both considered at least possibly related to the IMP.

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A

study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study termination or study site closure at any time after discussion with the Sponsor, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. However, dosing of a given participant may be suspended immediately on safety grounds pending discussion between the Investigator and Sponsor.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Significant violation of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.

Reasons for early termination of the study by the Sponsor or Investigator may include:

- Occurrence of serious or severe adverse event(s) considered to be related to the IMP.
- New information regarding the safety of the IMP that indicates a change in the risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for participants participating in the study.
- Discontinuation of further IMP development.
- New data become available regarding COVID-19, which raises concern for the safe study conduct so that continuation would pose potential risks to the participants or study site staff.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9 Publication Policy

The data generated by this study are considered confidential information and the property of Gedeon Richter Plc. This confidential information may be published only in collaboration with participating personnel from Gedeon Richter Plc. and in every case upon written consent from Gedeon Richter Plc. to publish the article. The publication of the results or presentation of the results at scientific meetings in whole or in part are within the sole and absolute discretion of the Sponsor. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to

provide comments. The Sponsor reserves the right to reject any article utilising any data generated by Parexel during the study before such article is presented or submitted for publication. The Sponsor will also not use Parexel's name in connection with any publication or promotion without the prior consent of Parexel. The Sponsor will comply with the requirements for publication of study results.

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.10 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first participant is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the participant benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.1.11 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all legal requirements. The civil liability of the Investigator, the persons instructed by him or her and the hospital, practice or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for participants participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

10.1.11.1 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare EDC/eCRF entries and individual participant's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. Electronic data capture/eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that participant confidentiality is maintained.

Checking of the EDC/eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audits/inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures Parexel and the Sponsor of the necessary support at all times.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the central laboratory with the exceptions specified at the end of the table.

According to local guideline or practice and upon the discretion of the Investigator, (preferably albumin-adjusted) serum calcium level may be measured prior to the administration of IMP or at any timepoint at local laboratory. The results, as well as the lower and upper limit of normal value of (albumin-adjusted) serum calcium at the local laboratory should be documented in the eCRF. Clinically significant abnormal values should be reported as an AE. However, for clinical study report purposes the values from the central laboratory will be considered.

Local laboratory tests can be done in the event that the central laboratory results are not available in time for IMP administration and the Investigator considers it as necessary for the safe administration of the IMP or for any other safety reason. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either an IMP decision or response evaluation, the results as well as the normal values must be entered into the eCRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1and 5.2 of the protocol.

- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 10-1 Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters	
Haematology	Platelet Count RBC Count with MCV, MCH and MCHC Haemoglobin Haematocrit	WBC count, Total with Differential (in absolutes and percentages): Neutrophils Lymphocytes Monocytes Eosinophils Basophils Large Unstained cells (if applicable)
Clinical Chemistry	BUN Creatinine Uric acid Creatine kinase eGFR using MDRD formula Glucose Potassium Sodium Calcium (Total) Albumin adjusted calcium	AST ALT Alkaline phosphatase GGT Total and direct bilirubin Total Protein Albumin Total cholesterol Triglyceride LDH

Laboratory Assessments	Parameters	
	Magnesium Phosphorus	CRP (high-sensitivity) Lipase
Routine Urinalysis	Specific gravity pH, Glucose, Protein, Blood, Ketones, Bilirubin, Urobilinogen, Nitrite, Leukocyte esterase Microscopic analysis will be performed if Blood, Protein, Leukocyte esterase or Nitrite is positive or if deemed necessary by the Investigator. Microscopic urine sediment examination (if required)	
Hormonal Tests	FSH (Screening only) TSH (Screening only) Vitamin D (25-hydroxyvitamin D) (Screening and day of IMP administration) PTH (Screening only)	
Serology Tests	Serology (HIV-1 and HIV-2 antibodies, anti-HBcAg total, HBsAg, anti-HBsAg and anti-HCV IgG and IgM)	
Bone Turnover Markers (PD marker)	sCTX Serum P1NP	
Immunogenicity Tests	Binding ADAs and NAbs	
Serum Drug Concentration	Denosumab concentration	
Note:	All study-required laboratory assessments will be performed by a central laboratory, with the exception of: • Dipstick urinalysis at all visits. • Immunogenicity and serum drug concentration samples (assessed by Sponsor).	

ADAs = anti-drug antibodies; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = c-reactive protein; eGFR = estimate glomerular filtration rate; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HBcAg = hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IMP = investigational medicinal product; LDH = lactate dehydrogenase MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration; MCV = mean corpuscular volume; MDRD = modification of diet in renal disease; NAbs = neutralising antibodies; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamic(s); PTH = parathyroid hormone; RBC = red blood cell count; sCTX = serum type I collagen C-telopeptide; TSH = thyroid-stimulating hormone; WBC = white blood cell count

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigational sites or other blinded personnel until the study has been unblinded.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

The definitions and procedures detailed in this document related to medical device events are in accordance with ISO 14155 [25].

10.3.1 Definition of Adverse Event

Adverse Event (or Adverse Experience) Definition
• An AE or adverse experience is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. • NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results, see Section 8.4.4 (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements, local tolerance, fracture assessment), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the Investigator (e.g., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after IMP administration even though it may have been present before the start of the study. • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the Adverse Event Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. However, fragility fractures will be considered as AEs.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition: Adverse Event Caused by Device Incident/Deficiency

- An AE caused by device incident/deficiency is any AE related to the use of a combination product [23, 24] or medical device. Adverse events caused by device incident/deficiency include AEs resulting from insufficient or inadequate instructions for use, AEs resulting from any malfunction of the device, or AEs resulting from use error or from intentional misuse of the device. Therefore, an AE caused by device incident/deficiency could be any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including an abnormal laboratory finding) in participants, whether or not related to the investigational medical device.

10.3.2 Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

A Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation • In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AE. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect

f. Other situations

- Medical or scientific judgement should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.
- Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other outcomes in the definition of serious (e.g., life-threatening experience, important medical event).
- Symptomatic overdose if it results in any of the serious outcomes listed above.
- Suicide attempt – with or without any sign or symptom – when considered to be threat of life.
- Neoplasia (benign or malignant) if judged to be medically serious.
- NOTE: In lethal cases, the cause of death shall be considered as an SAE and the death itself shall be considered as SAE outcome. Death may be indicated as an SAE if the cause has not been established. The Investigator should assess the event scientifically and medically and decide whether the event should be immediately reported to Parexel.

Definition: Serious Adverse Events Caused by Device Incident/Deficiency

- A serious adverse event caused by device incident/deficiency is defined as an adverse event that led to any of the following:
  - Death.
  - Serious deterioration in the health of the subject that resulted in any of the following:
    - life-threatening illness or injury,
    - permanent impairment of a body structure or a body function,

- hospitalisation or prolongation of patient hospitalisation,
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- chronic disease.

- Foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Definition: Unanticipated Serious Adverse Event Caused by Device Incident/Deficiency

- An unanticipated serious adverse event caused by device incident/deficiency is a serious adverse event caused by device incident/deficiency which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

10.3.3 Definition of Medical Device Events

Definition: Medical Device Events

A medical device event could be a device incident (in the case of Prolia®) or a device deficiency (in the case of RGB-14-P).

- A device incident is any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effects.
- A device deficiency is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

10.3.4 Recording and Follow-up of Adverse Event and Serious Adverse Event

Adverse Event and Serious Adverse Event Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Parexel in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. If a diagnosis is unknown, then the Investigator should report in detail signs and symptoms.
- For AEs caused by device incidents/deficiency, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE/SAE reported during the study and assign it to one of the following categories:

- Grade 1/Mild: The AE was an annoyance to the participant but did not further hinder baseline functioning; the AE may have been intermittent or continuous.
- Grade 2/Moderate: The AE caused the participant to experience some discomfort or some interference with normal activities but was not hazardous to health; prescription drug therapy may have been employed to treat the AE.
- Grade 3/Severe: The AE caused the participant to experience severe discomfort or severely limited or prevented normal activities and represented a definite hazard to health; prescription drug therapy and/or hospitalisation may have been employed to treat the AE.
- Grade 4/Life-threatening: The participant was at immediate risk of death form the event as it occurred.
- Grade 5/Death: The participant died due to the event.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. If AE severity or seriousness changed during its development, it should be recorded as a separate event.

Please see Table 8-1 for the assessment of intensity of injection site reactions.

Assessment of Causality

- The Investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgement to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Parexel. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Parexel.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Causal relationship should be assessed by answering the following question: "Is there a reasonable possibility the IMP caused the event?".

- Yes: There is a possible or probable relationship (i.e., there is a reasonable or strong temporal relationship, and the events are likely to be attributable to other drugs, underlying disease or other factors).
- No: The relationship is unlikely or non-existent (i.e., there is no strong temporal relationship and/or the use of other drugs, underlying diseases, or other factors provide plausible explanations for the event), or the participant did not take the investigational product.

Follow-up of Adverse Event and Serious Adverse Event (Caused by Device Incident/Deficiency or Not)

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE/SAE (caused by device incidence/deficiency or not) as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognised follow-up period, the Investigator will provide Parexel with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data on Follow-up SAE Report Form to Parexel immediately (but no later than 24 hours) of receipt of the information.

All AEs shall be followed up by the Investigator until resolution or the follow-up assessment, whichever comes first. Independently form the time of the next visit in case of AE the participant can revisit the Investigator. If, during follow-up, any non-serious AE worsen and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE. Data privacy rules should be adhered to.

To fully understand the nature of any SAE, it is important to obtain follow-up information. Follow-up reports must reported promptly within 24 hours or receipt. Whenever possible, relevant medical records such as discharge summaries, autopsy reports, medical consultations, and the like should be obtained. These records should be reviewed in detail, and the Investigator should comment on any event, laboratory

abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the participant's history.

In addition, all events or other findings determined to be SAEs should be identified on the follow-up SAE Report Form and the Investigator should assess whether it is related or not related to IMP. All SAEs are to be followed by the study staff until resolution or until the SAE is deemed stable.

It is the responsibility of the Investigator to report all relevant new information using the same procedures and timelines as those for the initial report. Serious adverse events occurring after the end of the study should be reported to the Sponsor/Parexel by the Investigator if the Investigator considers there a causal relationship with the IMP.

For instruction on follow-up of medical device related events see Section 6.1.2.

Action Taken to an Adverse Event

The Investigator will describe the action taken in the participant's source documentation and in the appropriate field of the eCRF. Action take to the AE will be documented as follows:

- None.
- Medication.
- Intervention.
- Medication and intervention.

Assessment of Outcome of Adverse Events

Outcome of an AE will be defined as:

- Recovered without sequelae.
- Recovered with sequelae.
- Not recovered (AE continuing).
- Recovering.

- Death.
- Unknown.

10.3.5 Reporting of Serious Adverse Events

Serious Adverse Event Reporting to Parexel via Electronic Data Collection Tool

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The Investigator shall report any SAEs and pregnancy cases immediately (within 24 hours of the Investigator's awareness) to Parexel. The Investigator is obliged to complete a separate SAE Report Form and Pregnancy Report Form in addition to the information in the eCRF.
- In particular, if the SAE is fatal or life-threatening, Parexel must be notified immediately, irrespective of the extend of available AE information.
- Parexel will then follow expedited reporting procedures according to local and international regulations as appropriate.
- The Investigator is obligated to pursue and provide information to Parexel on all SAEs in accordance with the timeframes and reporting specified above.
- In addition, the Investigator may be requested by Parexel to obtain specific additional follow-up information in an expedited fashion. In the case of a participants' death, a summary of available autopsy findings must be submitted as soon as possible to Parexel.
- The immediate report shall be followed by detailed written reports. The immediate and follow-up reports shall identify participants by unique code numbers assigned to the latter. For reported deaths, the Investigator shall supply the Sponsor and the local IECs with an additional information requested.
- For every AE, the Investigator should:
  - Provide a description (Investigator's verbatim term describing the event).
  - Provide dates of onset and resolution.
  - Assess the severity.
  - Provide the relationship to IMP.

- Provide the outcome.
- Provide action taken regarding IMP.
- Advise if other action (treatment, non-drug therapy) is required.
- Determination of "seriousness".

- Date and time of onset, outcome, date and time of off set and interventions, if applicable in case of each AE should be recorded.
- When calling Parexel's designated agent to report an SAE, state that you are reporting an SAE and give the Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title. Parexel's designated agent will then inform the Sponsor of the receipt of a new SAE.
- The Investigator and Parexel (or Parexel's designated agent) will review each SAE report and Parexel will evaluate the seriousness and the causal relationship of the event to IMP. In addition, Parexel (or Parexel's designated agent) will evaluate the expectedness according to the reference document (IB, SmPC or USPI). Based on the Investigator and Parexel's assessment of the event, a decision will be made concerning the need for further action.
- The Sponsor (Parexel on behalf of the Sponsor) has the legal responsibility to report, without delay to all Member States in which the clinical study is being conducted, including:
  - any SAE that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible,
  - any device event that might have led to a serious adverse event, if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate,
  - any new findings in relation to any event referred to in the above-mentioned bullet points.
- On behalf of the Sponsor, after Sponsor's approval, the Parexel Pharmacovigilance team shall report any medical device incident or deficiency that qualifies for a reportable medical device event according to the abovementioned criteria. The Parexel Pharmacovigilance team shall provide the Sponsor with local regulatory reporting requirement related to medical devices.

- After the study is completed, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- The contact details of Parexel International for reporting SAEs are PPD the contact details will also be specified on the SAE Report Form.
- If the site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information to the Sponsor's Clinical Safety Unit by telephone, fax or email. The contact details of the Clinical Safety Unit are provided below:

  PPD

  PPD

  PPD

  Phone: PPD

  Fax: PPD

  Email: PPD
- Further details on SAE/SUSAR reporting, including notification of Sponsor by Parexel after SAE/SUSAR events can be found in the SAE processing procedure and Global Safety reporting plan.

Serious Adverse Event Caused by Device Incident/Deficiency Reporting to Parexel

- NOTE: There are additional reporting obligations for medical device incidents/deficiencies that are potentially related to SAEs that must fulfil the local responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- Any medical device incidents/deficiencies that is associated with an SAE must be reported to Parexel immediately (but no later than 24 hours) after the determination that the event meets the definition of a medical device incident/deficiency associated with an SAE as it is described in the Addendum to Investigator Manual and the Product Complaint Procedure.

- The Investigator and Parexel (or Parexel's designated agent) shall review all device incidents/deficiencies and determine and document in writing whether they could have led to an SAE. The Investigator will remain blinded. These shall be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- The Sponsor is responsible for the final investigation of all device incidents/deficiencies.
- The contact details of Parexel International for reporting SAEs are PPD, the contact details will also be specified on the SAE Report Form.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any AE that is serious, associated with the use of the IMP, and unexpected (SUSAR) has additional reporting requirements, as described below.

- If the SUSAR is fatal or life-threatening, associated with IMP, and unexpected, regulatory authorities and IECs will be notified by Parexel within seven calendar days after Parexel learns of the event. Additional follow-up (cause of death, autopsy report and hospital report) information should be reported within an additional 8 days (15 days total).
- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with IMP, and unexpected, regulatory authorities and IECs will be notified within 15 calendar days after Parexel learns of the event.

Parexel shall inform the Investigators in the clinical study about the occurrence of SUSARs. All relevant follow-up information concerning SUSARs should be reported by Parexel to the regulatory authorities and IECs as soon as possible but within a maximum of 15 calendar days after Parexel learns of the event. Parexel on behalf of the Sponsor after Sponsor's approval will also provide annual safety updates to the regulatory authorities and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

The minimum information required for an initial report is:

- An identifiable Reporter.
- One single identifiable participant.
- At least one suspect adverse reaction.
- At least one suspect medicinal product.

However, as far as possible all points on the SAE form should be covered in the initial report, or the completed SAE form itself must be faxed to the Parexel Safety Contact. The original SAE form must then be sent by mail to the Parexel Safety Contact. In addition, the event must be document in the eCRF.

In case the Parexel Safety Contact cannot be contacted (e.g., out of normal working hours or at weekend), an automated reporting service is available. The required information should be faxed and a message should be left on the voicemail service (for phone/fax numbers see the numbers in the Section 10.3.5).

After receipt of the initial report, the safety centre will review the information and, if necessary, contact the Investigator, to obtain further information for assessment of the event. Parexel will be responsible for all information processing and reporting according to local legal requirements.

Details of the reporting procedures are determined in the Safety Management Plan.

10.4 Appendix 4: Coronavirus Disease 2019 (COVID-19) Related Considerations

Background to Coronavirus Disease 2019 (COVID-19)

There is currently an outbreak of COVID-19 caused by a novel SARS-CoV-2 that was first detected in Wuhan City, Hubei Province, China in 2019. This new virus has rapidly spread across the globe causing the World Health Organization to declare a pandemic situation on March 11, 2020. The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have impacted current and new clinical studies. As the threat of pandemic burden including new outbreaks, locally or globally, will impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect participants, site staff and society as a whole.

Both EMA [21] and FDA [22] as well as national health authorities in Europe have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws and local restrictions may change at high pace. Given the circumstances of potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in future, special attention will be paid to protect participants participating in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the newly issued EMA guideline.

Appropriate medical measures have been implemented into this protocol to detect COVID-19 disease to confirm eligibility of participants and to safely conduct the trial.

Restriction

Participants are advised to adhere to local requirements for reduction of the public SARS-CoV-2 exposure while ambulatory. All participants are called one day prior to every visit for assessing COVID-19 symptoms and signs and are asked not to attend the site in case of suspected infection. In addition, participants are asked for any contact with a person who has confirmed infection. If applicable, participants will be referred to the local health care system. Physical distancing and person-to-person contact restrictions will be applied and explained to participants while staying at the study site. Where physical distancing is not possible study participants will be asked to use surgical face masks and/or gloves if deemed appropriate by the Investigator and site staff and guided by local requirements.

10.5 Appendix 5: Abbreviations and Trademarks

ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AP	activator protein
AST	aspartate aminotransferase
AUEC	area under the effective curve
AUEC $sCTX_{0\text{-}m6}$	area under the effective curve after the first dose until Day 183 of %CfB in serum type I collagen C-telopeptide
BLQ	below the limit of quantification
BMD	bone mineral density
BMI	body mass index
%CfB	percent change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	coronavirus disease 2019
CRO	contract research organisation
DXA	dual energy X-ray absorptiometry
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form(s)
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
FAS	full analysis set
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
GnRH	gonadotropin-releasing hormone

HBcAg	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IMP	investigational medicinal product
INN	international non-proprietary names
IRB	Institutional Review Board
IRT	interactive response technology
MAPKs	mitogen activated protein kinases
MCAR	missing completely at random
M-CSF	macrophage-colony stimulating factor
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed model for repeated measures
MNAR	missing non at random
NAbs	neutralising antibodies
NK	nuclear factor
OC	osteoclast
ODF	osteoclast differentiation factor
ONJ	osteonecrosis of the jaw
OPGL	osteoprotegerin ligand
P1NP	procollagen type 1 N-terminal propeptide
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PTH	parathyroid hormone
RANK	receptor activator of nuclear factor kappa-B
RANKL	receptor activator of nuclear factor kappa-B ligand
SAE	serious adverse event
SAP	statistical analysis plan

SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
sCTX	serum type I collagen C-telopeptide
SD	standard deviation
SERM	selective oestrogen receptor modulator
SmPC	Summary of Products Characteristics
SoA	schedule of activities
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse events
TNF	necrosis factor
TRAF	TNF receptor associated factor
TRANCE	TNF related activation induced cytokine
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
USPI	US package insert

10.6 Appendix 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Non-substantial Amendment 1: 20 Jul 2021

Overall Rationale for the Amendment

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

Non-Substantial Amendment 1 Summary of Changes:

Section # and Name	Description of Change*	Brief Rationale
1.3 Schedule of Activities	Reference 'm' of Table 1-1 and Reference 'k' of Table 1-2 amended as follows: "Injection site reaction assessment should be done predose and **approximately** 1 hour postdose~~,~~ **during this 1 hour period. Any further assessment of the injection site or prolonged observation of the participant may be done at the discretion of the Investigator**.~~ At the discretion of the Investigator another assessment of the injection site may be done after the initial 1 hour."~~	Amended following suggestion from the Czech Republic Regulatory Authority.
6.3.3 Blinding and breaking the blind	Third paragraph of section amended as follows: **The Investigator should make an effort to contact the Parexel Medical Monitor, if possible, prior to unblinding.**~~ If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact Parexel Medical Monitor prior to unblinding a participant's study treatment assignment unless this could delay emergency treatment of the participant. If this is not possible and the situation is an emergency the Investigator or his/her delegated deputy may break the blind and contact Parexel as soon as possible thereafter.~~	Amended following suggestion from the Czech Republic Regulatory Authority.

Section # and Name	Description of Change*	Brief Rationale
6.3.3 Blinding and breaking the blind	Fifth paragraph of section amended as follows: **In all unblinding cases, Parexel should contact the Sponsor as soon as possible.** ~~In all unblinding cases, Parexel should contact the Sponsor prior to or as soon as possible (< 24 hours) after unblinding.~~	Amended following suggestion from the Czech Republic Regulatory Authority.
8.4.5. Local Tolerance (Skin Examination)	First paragraph of section amended as follows: On dosing days, injections site reaction assessment should be done predose (i.e., for exclusion of a pre-existing, not IMP injection induced condition) and **approximately** 1 hour postdose**;** ~~. At~~ **during this 1 hour period (i.e., from dosing to the injection site assessment) the participant will stay in the clinic for general safety observation. Any further assessment of the injection site or prolonged observation of the participant may be done at the discretion of the Investigator**~~another assessment of the injection site may be done after the initial 1 hour~~.	Amended following suggestion from the Czech Republic Regulatory Authority.

* **Bolded text** is added text, ~~struck-through text~~ is deleted text.

Substantial Amendment 1: 03 Aug 2021

This amendment is 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 is mainly amended to incorporate and implement responses and suggestions made by the United States Food and Drug Administration.

Substantial Amendment 1 Summary of Changes:

Section # and Name	Description of Change	Brief Rationale
Sponsor signatory page	Sponsor signatories were amended.	Sponsor request.
1.1 Synopsis 1.3 Schedule of Activities (SoA) 2.2.1 Risk Assessment 3 Objectives and Endpoints 8.3.3 Fracture Assessment 8.3.3.2 Non-vertebral Fracture 8.4 Safety Assessments 9.4.4.3.2 Other Safety Data 10.1.7 Source Documents 10.3.1 Definition of Adverse Event	Text added and updated to include fracture assessment as adverse event evaluation.	Amended following suggestion from the United States Food and Drug Administration (US FDA).
1.3 Schedule of Activities (SoA) 2 Introduction 6.1 Study Treatments Administered 6.1.1 Study Treatment Devices 6.1.2 Device-related Complaints 6.3.3 Blinding and Breaking the Blind 8.5 Adverse Events and Serious Adverse Events 8.5.3 Follow-up of Adverse Events and Serious Adverse Events 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Text added to specify recording device-related events.	Amended following suggestion from the US FDA.
Section 6.1 Study Treatments Administered (Table 6-1)	Packaging and Labelling updated to Device Description and additional information relating to devices added.	Clarification of devices.
1.3 Schedule of Activities (SoA)	Period for submission of dual energy X-ray absorptiometry and X-ray imaging for central independent review increased to 10 days.	Increased to allow for sufficient time for review.
1.3 Schedule of Activities (SoA) 8.4.4 Clinical Safety Laboratory Assessments	Text amended to specify urine sample analysis in case of abnormal results may be sent to the central laboratory if deemed necessary by Investigator.	Text added for clarification.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) 8.4.5 Local Tolerance (Skin Examination)	Text amended to better clarify observation period of injection site post investigational medicinal product administration.	Amended for clarification.
1.3 Schedule of Activities (SoA) 9.4.1 General Considerations	Baseline value for bone mineral density (BMD) clarified.	Amended following suggestion from the US FDA.
2.2.1 Risk Assessment	Text added on serious adverse reaction and reporting of suspected unexpected serious adverse reactions.	Text added at Sponsor request.
2.2.1 Risk Assessment 11 References	Text added post-marketing experience with US Prolia.	Amended for consistency with latest Prescribing Information.
2.2.1 Risk Assessment	Text added to indicate Investigator responsibility for coronavirus disease 2019 testing in symptomatic and asymptomatic participants.	Text added for clarification.
5.2 Exclusion Criteria	Text added on inclusion/exclusion of participants with a history of childhood rickets.	Text added for clarification.
5.2 Exclusion Criteria	Text added to specify described uncontrolled hypo- and hyperthyroidism.	Text added for clarification.
5.2 Exclusion Criteria	Text added to further clarify exclusion criteria with regards to osteonecrosis of the jaw.	Text added for clarification.
5.2 Exclusion Criteria 6.5.1 Prohibited Therapy	Update to excluded medication prior to and during the study.	Text added for clarification.
5.4 Screen Failures	Text added to indicate participants retested for vitamin D and calcium testing will not be classified as screen failures.	Text added for clarification.
1.1 Synopsis 4.1 Overall Design 6.3.3 Blinding and Breaking the Blind	Text removed for consistency of responsibilities of treatment and unblinding throughout the protocol.	Amended for clarification.
6.5.2 Additional Study Treatment	Text added to specify procedures to following in the case of intolerance to non-investigational products.	Text added for clarification.
6.7 Intervention After the End of the Study	Text amended to clarify risks associated with denosumab discontinuation and actions to be taken after study treatment discontinuation.	Text amended to further clarify risks and actions to be taken.
7.1 Discontinuation of Investigational Medicinal Product, Participant Discontinuation/Withdrawal from the Study	Text added to address management of reduction in BMD below a pre-defined threshold that may occur during the study.	Amended following suggestion from the US FDA.
	Text added to establish individual stopping criteria (e.g., life-threatening treatment-related hypersensitivity/allergic reaction).	Text added for clarification.
8.4.1 Physical Examinations	Text updated to clarify timing of height assessment.	Text added for clarification.
8.7 Immunogenicity Assessment 8.8 Serum Drug Concentration	Text removed for clarification.	Clarification of text.

Section # and Name	Description of Change	Brief Rationale
9.3 Population for Analysis 9.4.2 Estimands 9.4.5 Handling of Missing Data	Text updated to reduce the number of participants who discontinue the study early and the amount of missing data.	Amended following suggestion from the US FDA.
9.4.2 Estimands	Text updated to include all randomisation stratification factors in analysis model.	Amended following suggestion from the US FDA.
10.2 Appendix 2: Clinical Laboratory Tests	Removal of erythrocyte sedimentation rate.	Removed from haematology panel as not performed by central laboratory.
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 11 References	References added for device-related complaints definitions and procedures.	Amended at Sponsor request.
10.3.1 Definition of Adverse Event	Definition updated to be in line with the International Council for Harmonisation Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).	Amended at Sponsor request.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

Substantial Amendment 2: **10 Jan 2022**

This amendment is 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 is mainly amended to incorporate and implement changes for statistical analysis, consistency with supporting study documents and suggestions made based on Investigator experiences.

Substantial Amendment 2 Summary of Changes:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 3 Objectives and Endpoints (Table 3-1)	Added text to specify primary pharmacodynamic endpoint secondary for the United States Food and Drug Administration (US FDA) submission.	Text added for clarification.
1.1 Synopsis; 4 Overall Design; 6.3.3 Blinding and Breaking the Blind	Added text to specify blinded and unblinded staff during the Main and Transition Periods for reporting purposes.	Text added for clarification.
1.3 Schedule of Activities (Table 1-1)	Deleted pre-visit phone call for Screening visit.	Participants will not be contacted before the Screening visit to assess coronavirus disease 2019 symptoms and signs.
1.3 Schedule of Activities (Table 1-1 and Table 1-2)	Added footnote to specify dual energy X-ray absorptiometry should be performed before dosing at Week 26 and Week 52.	Text added for clarification.
1.3 Schedule of Activities (Table 1-1 and Table 1-2); 2.2.1 Risk Assessment; 6.1.2 Medical Device Events; 6.3.3 Blinding and Breaking the Blind; 6.4 Investigational Medicinal Product Compliance; 8.5 Adverse Events and Serious Adverse Events; 8.5.1 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Event Information; 8.5.3 Follow-up of Adverse Events and Serious Adverse Events; 10.3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Text and terminology amended to align with the Product Complaint Procedure document.	Text amended for clarification.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (Table 1-1); 2.2.1 Risk Assessment; 10.2 Clinical Laboratory Tests (Table 10-1)	Text amended or deleted for severe acute respiratory syndrome coronavirus-2 testing to specify as required by local regulation.	Text amended or deleted as infection may occur at any time during the study and should be assessed as required by local requirements.
1.3 Schedule of Activities (Table 1-1); 8.2.5 Screening Assessment	Text added to specify the Screening visit may be conducted over more than 1 day during the Screening period, as required for logistical reasons.	To extent Screening period to allow required time to perform all requirement assessments to determine participant eligibility for study participation.
5.2 Exclusion Criteria	Updated exclusion criterion for participants with inadequate renal and hepatic function (exclusion criterion 25) to specify exception for participants with Gilbert's syndrome.	Text added for clarification.
5.2 Exclusion Criteria; 6.5.1 Prohibited Therapy	Added antioestrogens, aromatase-inhibitors, low molecular weight heparins, vitamin K, vitamin K antagonists (e.g., warfarin, acenocumarol), emtricitabine, tenofovir, adefovir and pregabalin as prohibited medication.	Pregabalin, antioestrogens, aromatase-inhibitors, low molecular weight heparins, vitamin K antagosists (e.g., warfarin, acenocumarol), emtricitabine, tenofovir added to list of prohibited medication due to potential effect on bone.
5.2 Exclusion Criteria; 7.1 Discontinuation of Investigational Medicinal Product, Participant Discontinuation/Withdrawal from the Study	Added pregnancy and breastfeeding as exclusion criteria and breastfeeding under discontinuation/withdrawal criteria.	Added as per request from Italian Ethics Committee.
5.2 Exclusion Criteria; 10.2 Clinical Laboratory Tests	Amended text to specify hepatitis B exclusion criteria.	Text amended for clarification.
8.2.4 Prior and Concomitant Medication Review	Text updated to define prior and concomitant medication timeframe.	Text updated for consistency with Section 6.5.
8.5 Adverse Events and Serious Adverse Events	Text added to specify medical device events that cause adverse events (AEs) and serious adverse events (SAEs) will be reported following the same periods and procedures as study AEs and SAEs.	Text added for clarification.
8.5.4 Regulatory Reporting Requirements for Serious Adverse Events; 9.4.4 Additional Analyses; 10.3.5 Reporting of Serious Adverse Events	Added text on reporting device events to all Member States in which clinical study is being conducted.	Text added for clarification.

Section # and Name	Description of Change	Brief Rationale
9.1 Statistical Hypotheses; 9.2 Sample Size Determination; 9.4.1 General Consideration; 9.4.2 Estimands; 9.4.2.1 Supplementary (tertiary) estimands; 9.4.4.3 Safety; 9.4.5 Handling of Missing Data	Text added and updated to clarify study hypotheses, study estimands and statistical analysis of safety and handling of missing data.	Text amended for clarification.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

Substantial Amendment 3: **19 Jan 2023**

This amendment is 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:

This protocol is 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 United States (US) Food and Drug Administration (FDA), considering the drop-out is higher than expected.

Substantial Amendment 3 Summary of Changes

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema (Figure 1-2) 4.1 Overall Design 6.1 Study Treatment Administered (Table 6-1) 6.3.2 Re-randomisation and Participant Subset in Transition Period 9.2 Sample Size Determination	Amended text to implement 10% increase of the number of participants to be enrolled during the Transition Period than previously.	Participants might withdraw the consent right after the Main Period that would trigger lack of data from follow-up visits.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

11 References

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Investigator Agreement Page

Declaration of the National Coordinating Investigator

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

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in 2013 and the guidelines on GCP.

National Coordinating Investigator

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

Declaration of the Investigator

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

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, EDC system/electronic CRF (eCRF), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted IRB or IEC. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the participants.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the Local Study Centre

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number