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

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Gedeon Richter Plc.

RGB-14-101

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

Statistical Analysis Plan

Version: 1.0

Parexel Project Number: 252679

Sponsor Signature Page

This document has been approved and signed electronically on the final page by the following:

Approved by: _____ _____

PPD *Date*

PPD

Gedeon Richter Plc.

Approved by: _____ _____

PPD *Date*

PPD

Gedeon Richter Plc.

Approved by: _____ _____

PPD *Date*

PPD

Gedeon Richter Plc.

Parexel Signature Page

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD PPD

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Version History

SAP Version	Date	Change	Rationale
Draft 0.1	28 Jan 2022	Document creation	First draft
Draft 0.2	16 Nov 2022	Major	Use of newest PAREXEL template, based on TransCelerate common statistical analysis plan (version 2.0). Comments implementation. In deep details added for pharmacodynamic and immunogenicity analysis.
Draft 0.3	17 March 2023	Major	Updates to accommodate new eCRF version 5 and new Protocol Amendment 5
Draft 0.4	28 April 2023	Major	Updates in the primary analysis strategy due to protocol amendments in protocol version 5.0 from Protocol Amendment 5
Draft 0.5	20 July 2023	Minor	Fix of client comments & minor refinements
Draft 0.6	17 August 2023	Minor	Minor refinements and removal of SUSAR from safety section
Draft 0.7	05 October 2023	Minor	Adding new requested safety summaries, reverting the definition of significant ADA titre increase back to the fold increase instead of using the minimal significant ration (MSR)
Draft 0.8	27 October 2023	Minor	Minor refinements
Draft 0.9	07 November 2023	Major	Request to changes in the logics for handling out of schedule assessments, with major impact on mapping analysis visits.

			Request to add additional sensitivity analysis for secondary efficacy endpoint of vertebral fracture.
Final 1.0	Date of last signature	Minor	Fix of last comments and document finalization

1 Introduction

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 in healthy volunteers as well as a comparative efficacy and safety study between RGB-14-P and Prolia® in women with postmenopausal osteoporosis. Although the comparative PK/PD study will commence earlier, essentially the two studies will run in parallel.

The primary outcome of this study is determined based on the results of the efficacy analysis at Week 52 (please refer to section 4.2.1). 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 are described in the Blinding Maintenance Plan.
The Main Clinical Study Report will be completed based on the data obtained after all participants have either completed the Week 52 study visit or discontinued the study. The data obtained in the Transition Period will be added as a Final/Supplemental Clinical Study Report.
In this statistical analysis plan (SAP), analyses will be presented separately for the main and the transition period, and separate sets of Tables, Figures and Listings (TFLs) will be produced for the main and transition period.
In particular:

- ➔ EMA submission is required at 12 months; EMA will receive CSR based on 12 months data (main period)
- ➔ FDA submission required at 18 months; FDA will receive CSR based on whole study data (main + transition period).

The main CSR for EMA submission and the final/supplemental CSR for FDA submission will be supported by two different sets of SDTMs and ADAMs. Full regular SDTM and ADAM will

include all the study data and will be used when running analysis for FDA submission, while SDTM_Main (i.e., the '_main' extension will be added to each domain) and ADAM_Main (again, the '_main' extension will be added to each dataset) will include only the data belonging to the main period and will be used when running analysis for EMA submission.
For main period CSR, TFLs will include an identifier for the main period data cut off and will include "for main period" on the analysis set (i.e. Full Analysis Set for Main Period).
For final/ supplemental CSR, TFLs will be executed on the full regular datasets and will include data cut off and identification of main / transition period as relevant on the analysis set (i.e:. "Full Analysis Set for Main Period" or "Full Analysis Set for Transition Period") as appropriate.
Two different Blinded Data Review Meetings (BDRM) and database locks (DB Lock) will happen, one covering the main period and one covering the transition period. General unblinding will happen after the last DB Lock, i.e., the transition period one. A separate unblinded team may be assigned at Parexel to proceed with unblinding TFLs production in between the two DB Locks.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 5.0 (March 28th, 2023)
- electronic Case Report Form (eCRF), Version 5.0 (March 21th, 2023)
- Blinding Maintenance Plan, Version 3.0 (Nov 15th, 2023)
- Global Data Operation (GDO) Plan, Version 3.0 (12th December,2023)

The structure and content are based upon International Conference on Harmonisation (ICH) requirements as detailed in

- ICH E3 Structure and Content of Clinical Study Reports [1]
- ICH E9 Statistical principles for Clinical Trials [2]
- ICH E9(R1) Addendum on estimands and sensitivity analysis in clinical trials [3]

The SAP details the statistical methodology to be used in analysing study data and outlines the statistical programming specifications for the TFLs. It describes the variables and populations,

anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP). In case of discrepancies between CSP and SAP, these will be documented in section 4.8 of the SAP and the SAP supersedes the CSP.

1.1 Objectives, Endpoints, and Estimands

Table 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 sCTX0-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

Objectives	Endpoints
	• 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 • Titer 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

Primary and Secondary estimand(s)

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

Table 2 – Summary of the Primary and Secondary Estimands

Estimands	Primary: Treatment Policy Estimand (TPE)	Secondary: Principal Stratum Estimand (PSE)
Clinical questions of interest	Do RGB-14-P and US-licenced 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-licenced 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 have not experienced any ICEs on either treatment arms?
Variable	Percent increase in BMD in lumbar spine from Baseline to Week 52, i.e., %CfB, is the primary study endpoint and is defined in Section 4.2.1.1 (%CfB = (Post Baseline – Baseline) / Baseline * 100).	
ICE	ICE1: The first and/or the second dose of randomised IMP is not administered. ICE2: The participant received other medication alongside the IMP, which affects the primary variable (please refer to protocol section [Prohibited Therapy]).	
ICE strategy	ICE1: Treatment policy strategy will be applied: All obtained data points will be included in the analysis, 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. In other words, responses obtained after ICE occurrence will be imputed with multiple imputation techniques so that outcomes observed after ICE2 occurrence will be modelled under the null hypothesis.	Principal stratum causal estimand strategy will be used: Only patients who would not experience either ICE if exposed to either treatment are relevant to the clinical question. To control the validity of the estimand dropout and ICE rates and reasons will be monitored.

Estimands	Primary: Treatment Policy Estimand (TPE)	Secondary: Principal Stratum Estimand (PSE)
Treatments	Test product: RGB-14-P subcutaneous injection 60 mg. Reference product: Prolia® subcutaneous injection 60 mg.	
Study Population	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, as far as ICE1 and ICE2 are not met.
Main estimator	For EMA submission (details in sections 4.2.1.2.1 and 4.2.1.2.1.1): δ will be estimated by using ANCOVA model (SAS PROC GLM) with the following factors: 1. Randomised treatment 2. Baseline BMD value 3. Previous use of bisphosphonates 4. Geographical region 5. Machine type 6. Machine type * Baseline BMD value interaction Missing data will be assumed to be MCAR and will not be imputed (details in section 4.2.1.2.1.1).	δ will be estimated by using ANCOVA model (SAS PROC GLM) with the following factors: 1. Treatment 2. Baseline BMD value 3. Previous use of bisphosphonates 4. Geographical region 5. Machine type 6. 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

Estimands	Primary: Treatment Policy Estimand (TPE)	Secondary: Principal Stratum Estimand (PSE)
	For US FDA submission (details in sections 4.2.1.2.1 and 4.2.1.2.2): δ will be estimated by using ANCOVA model (SAS PROC GLM) with the following factors: 1. Treatment 2. Baseline BMD value 3. Previous use of bisphosphonates 4. Geographical region 5. Machine type 6. 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 in section 4.2.1.2.1.2)	randomisation, the strategy analysis with MI will be followed. Details in section 4.2.1.2.2.
Sensitivity estimator	For EMA submission (details in sections 4.2.1.2.1.1 and 4.2.1.3.1): As a sensitivity estimation for the primary analysis of the primary endpoint, missing data may be imputed using MI rules, techniques proposed by Jakobsen et al, 2017 will be considered [4]. 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	Due to the parallel design, robustness of the estimator will be assessed by tipping point analysis [5]. Details in section 4.2.1.3.3.

Estimands	Primary: Treatment Policy Estimand (TPE)	Secondary: Principal Stratum Estimand (PSE)
	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 section 4.2.1.3.2.	

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; IMP = investigational medicinal product; ITT = intent-to-treat; MCAR = missing completely at random; MI = multiple imputation; MNAR = missing non at random; PPS = per protocol analysis set; US = United States

1.2 Study 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 efficacy 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 and Figure 2). Day 1 of Treatment Periods 2 and 3 is 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 for efficacy, PD, immunogenicity and safety assessment as indicated in the Schedule of Activities (Table 10 and Table 11).

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 post dose during Treatment Period 1
- Days 1, 8, 15, 30 and 90 post-dose during Treatment Period 2

An End of Study Visit is planned on Day 183 (Week 52) post-dose during Treatment Period 2 for participants not continuing participation in Transition Period. Please see Protocol 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 180 participants will enter the Transition Period. A subset of approximately 120 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 60 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.

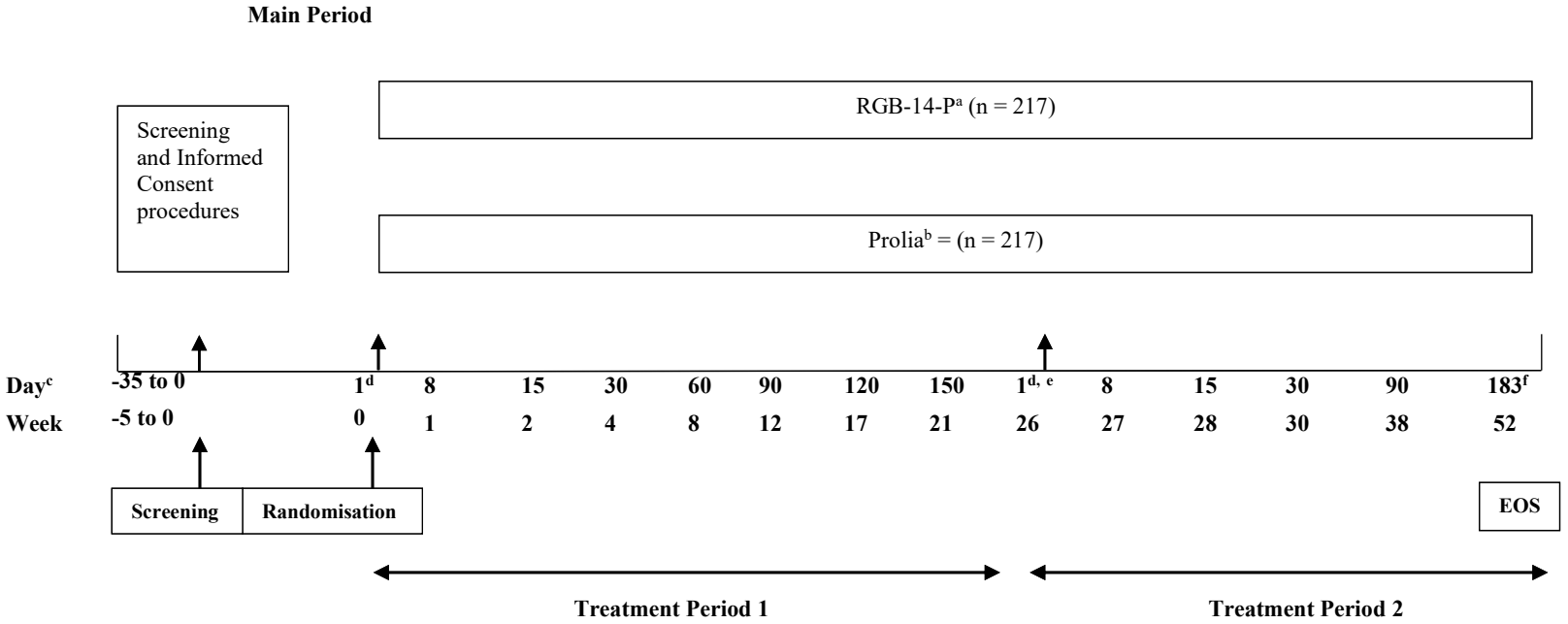
Visits during the Transition Period:

- Days 1, 8, 15, 30 and 90 post-dose during Treatment Period 3

An End of Study Visit is planned on Day 183 (Week 78) post-dose during Treatment Period 3. Please see Protocol 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.

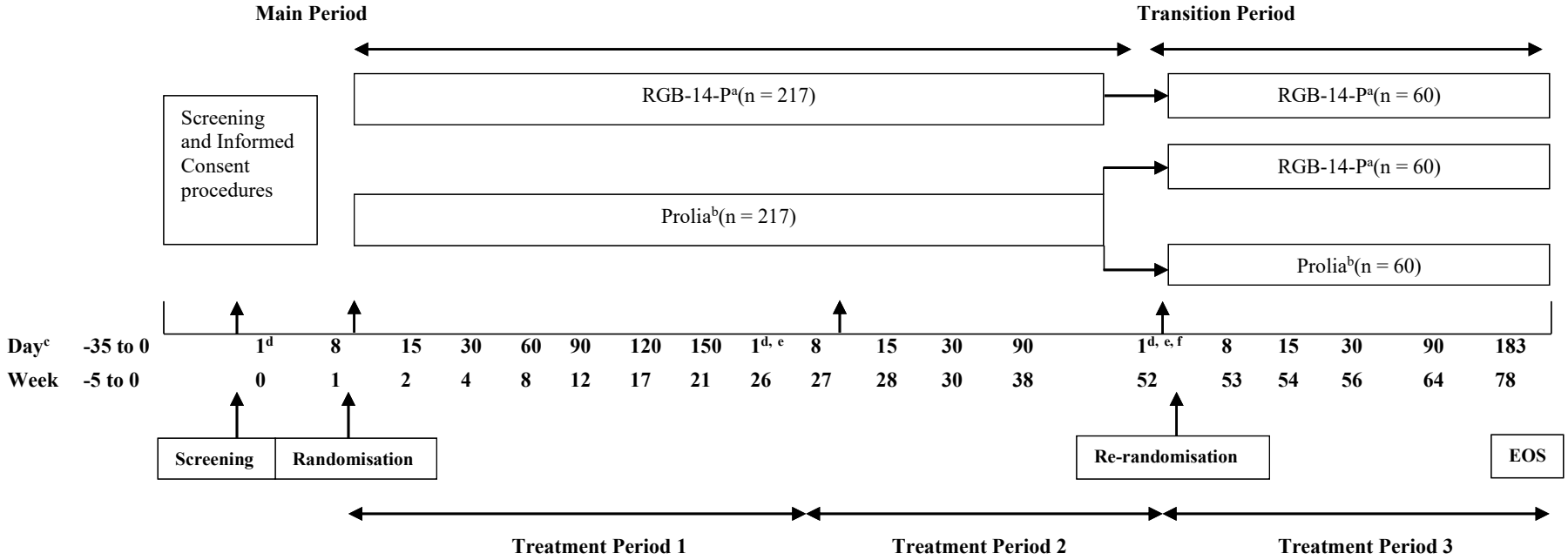
Figure 1 – Scheme of Study Design - Main Period only



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 2

Figure 2 – Scheme of 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.

2 Statistical Hypotheses

This study is designed to test for bio-equivalence of RGB-14-P and Prolia®. 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. CCI [redacted] is considered for this study, as per sample size determination considerations at section 5 of this SAP.

- ***Efficacy estimand for EMA submission***

  CCI [redacted]

  CCI [redacted]

  where:

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

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

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

  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:

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

  CCI [redacted]

  CCI [redacted]

  Significance level = 0.05 (one sided)

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

  CCI [redacted]

  CCI [redacted]

  Significance level = 0.05 (one sided)

  where:

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

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

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

Overall, RGB-14-P will be claimed to be equivalent to Prolia® in the event that both $H_{0(non\text{-}inf\ test)}$ and $H_{0(non\text{-}sup\ test)}$ are rejected.

- ***PD endpoint***

According to bioequivalence criteria, the AUEC variability can range from −20% to +25% between the generic and the reference product [6] [7]. Bioequivalence criteria margin of 80.00–125.00% are recognised by several regulatory authorities worldwide [7].

Null Hypothesis H0: Geometric Mean Ratio (GMR) of AUEC $sCTX_{0\text{-}m6}$ (GMR, RGB 14-P / Prolia®) not contained within [80.00%, 125.00%]

Alternative Hypothesis H1: GMR of AUEC $sCTX_{0\text{-}m6}$ (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.

2.1 Multiplicity Adjustment

FDA submission

Evaluation of the primary objective is uniquely based on primary efficacy endpoint; no multiplicity concern raises.

EMA submission

Similarity between RGB-14-P and Prolia® will be assessed based on the simultaneous success of hypothesis tests for all primary endpoints (Efficacy and Pharmacodynamics). Endpoints will then be seen as co-primary, thus alpha adjustment is not needed for this coprimary endpoints study.

3 Analysis Sets

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

Table 3 – Populations for Analysis

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

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

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

Unless otherwise specified, the analysis sets will serve as below:

- ENR for subject disposition
- FAS for demographic and baseline characteristics, medical history, medications, efficacy (with the exception of secondary estimand)
- PPS for efficacy secondary estimand
- SAF for exposure and safety

- PDS for pharmacodynamic
- IAS for immunogenicity

In general, in ENR and in FAS data of subjects will be listed and summarised under the planned treatment, independently of total amount of the treatment received; while in SAF, PPS, PDS and IAS, data of subjects will be listed and summarised under the treatment actually received, independently of total amount of the treatment received.
Cases where a different than assigned treatment kit was injected, should be known prior to unblinding as these can be identified by a reconciliation process comparing the allocated kit number available in the IRT reports and the injected kit number reported into the EDC.
However, it will not be known until unblinding if the injected kit was of the same treatment as the assigned kit. Therefore, cases of discrepancies and corresponding handling strategies will be discussed at a BDRM both pre- and post-unblinding. If any subjects receive a different treatment at Treatment period 1 compared to Treatment period 2, the effect on the SAF, PPS, PDS and IAS period 2 TFLs will be discussed, and possible data handling strategies agreed.

4 Statistical Analyses

4.1 General Considerations

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.
Two deliverables are expected: one for the main and one for the transition period. In general, outputs delivered for the main period will contain subject data collected before the eventual transition period randomisation; while outputs delivered for the transition period, will contain data collected during both the main and transition period. More details are provided below in sections 4.1.5, 4.1.6 and 4.1.7.
The overall outline of the scheduled assessment and other study procedures can be found in SoA (Table 10 and Table 11). The data handling conventions should be interpreted within the framework of the SoA. All tables, listings, and graphs will be produced to landscape orientation using Courier New 9pt font and will be incorporated into a MS Word document as a (RTF) rich text file (margins on standard A4: Margins (top, left, right, and bottom) 2.54 cm.

4.1.1 Analysis Conventions

Continuous data will be summarised in terms of the mean, standard deviation (SD), median, minimum, maximum, quartiles and number of observations, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.
Categorical data will be summarised in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only. Changes from baseline in categorical data will be summarised using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values lower than 0.001 will be presented as "<0.001".

Confidence intervals will be presented to one more decimal place than the raw data.

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.

4.1.2 Study Days

Study Day in Treatment Period 1 (Main Period)

The date of IMP administration for Treatment Period 1 is defined as Day 1 Week 0.

In Treatment Period 1, other study days are defined relative to the Study Day 1 as follow:

- assessments taken before the Treatment Period 1 IMP administration:
  Relative Study Day = assessment date - Treatment Period 1 IMP administration date
- assessments on or after the Treatment Period 1 IMP administration:
  Relative Study Day = assessment date - Treatment Period 1 IMP administration date + 1

In Treatment Period 1, study days will be identified as 'TP1DX', as an example IMP administration at Week 0 will be TP1D1.

Study Day in Treatment Period 2 (Main Period)

Day 1 Week 26 refers the IMP administration in Treatment Period 2: in Treatment Period 2, Study Day 1 is defined as the date of IMP administration occurring on Treatment Period 2.

In Treatment Period 2, study days will be identified as 'TP2DX', as an example IMP administration at Week 26 will be TP2D1.

In Treatment Period 2, other study days are defined relative to the TP2D1 as follow:

- assessments taken on or after Treatment Period 1 and before the Treatment Period 2 IMP intake, the Relative Study Day of Treatment Period 1 apply
- assessments on or after the Treatment Period 2 IMP administration:
  Relative Study Day = assessment date - Treatment Period 2 IMP administration date + 1

Study Day in Treatment Period 3 (Transition Period)

The date of IMP administration for Transition Period is defined as Day 1 Week 52: in Transition Period, Study Day 1 is defined as the date of IMP administration occurring on the Transition Period.

In Transition Period, study days will be identified as 'TP3DX', as an example IMP administration at Week 52 will be TP3D1.

In Transition Period, other study days are defined relative to the TP3D1 as follow:

- assessments taken on or after Treatment Periods 1 and 2 and before the Transition Period IMP intake, the Relative Study Day of Treatment Periods 1 and 2 apply
- assessments on or after the Transition Period IMP administration:
  Relative Study Day = assessment date - Transition Period IMP administration date + 1

4.1.3 Study Visits

Study visits will be presented in the format "TPX Day X – Week X".

In general, assessments will be listed and summarised under the visit in which they were collected. However more detailed rules for presenting aggregated summaries are described below in this SAP section 4.1.6. This general rule apply to the treatment injection visits as well in consideration of assessments scheduled to be performed both pre and post-dose: in other words, both the pre-dose physical examination and the post-dose skin examination collected on the day of the first injection will be listed and summarised in visit 'TP1 Day 1 - Week 0'; with same rule applying on the day of the second injection.

In general, if not stated otherwise, if subject came on site for week 26 visit, is not treated with second injection and is discontinued from the study, her week 26 collected assessments will still be reported under visit 'TP2 Day1 - Week 26'.

Details about presentation of results collected on study Week 52 are detailed below.

Handling of study Week 52 data collection

Study Week 52 represents TP2 Day 183 - Week 52 visit for all the subjects.

Furthermore, for subjects enrolled into the transition period, such a visit also represents TP3 Day1; for analyses purpose, for these subjects, visit of Week 52 will be considered as both TP2 Day 183 - Week 52 and TP3 Day 1 - Week 52.
In general, for subjects enrolled into the transition period:

- in the study visit listing, the date of Week 52 will appear twice: once for TP2 Day183, once for TP3 Day1
- in the listings for the assessments not directly related to the injection and performed before third injection, results will be presented under TP2 Day183 and corresponding treatment
- in the main period tables for the assessments not directly related to the injection and performed before third injection, results will be presented under TP2 Day183 and the corresponding treatment
- in the transition period tables for the assessments not directly related to the injection and performed before third injection, results will be presented under TP2 Day183 and corresponding treatment; in these tables, TP3 Day1 visit will not be presented

Specific rules for reporting of the assessments scheduled at Week 52 for subjects enrolled into the transition period are reported in Table 4.

Table 4 – Assessments scheduled at Week 52 for subjects enrolled into the transition period

Assessment	Handling in listing	Handling in table
Procedure(s)/assessment/blood collection to be performed predose[a]		
- Inclusion/Exclusion Criteria Assessment for the Transition Period - Re-randomisation - Pre-visit Phone Call	Listed under visit as received from eCRF data.	Summarised in transition period tables only, as TP3 assessment.
- Weight, Height, BMI - Physical Examination - Haematology and Clinical Chemistry - Urinalysis - 12-lead ECG - Vital Signs - DXA Scan Assessment (collected up until 10 days after 3rd injection as explained in above section 4.2.1.1 of this SAP) - Lateral Spine X-ray - Immunogenicity (binding ADAs and NAbs) Sampling - Serum Drug Concentration Sampling - PD (Serum CTX and P1NP) Samplings	Listed under visit as received from eCRF data.	Main and transition period tables: summarised under TP2 Day183. Transition period tables: TP3 Day1 visit will not be presented.
Procedure(s)/assessment related to the dosing		
- IMP Administration - Participant Identification and Visit Reminder Card - Medical Device Events - Local Tolerance (Skin Examination)[b]	Listed under visit as received from eCRF data.	Summarised in transition period tables only, as TP3 procedure/evaluation.

[a] When time of assessment is collected, this will be compared to the treatment period injection date time to establish if the assessment was taken before injection. If time of assessment is not available then the assessment is assumed to be taken before injection, unless clear evidence that it wasn't.
[b] Injection site reaction assessment should be done pre-dose and approximately 1-hour post-dose.

4.1.4 Definition of Baseline

Unless otherwise specified, baseline will be taken as the last available assessment prior to first IMP dosing on Treatment Period 1, Day 1 Week 0.

4.1.5 Data Listings

All original and derived parameters will be listed.
All listings will include scheduled and unscheduled measurements.
Unless specified otherwise, data in listings will be organized for Treatment Periods (Treatment Period 1 and 2) and Transition Period.
In general, listings will be sorted by treatment arm allocation (RGB-14-P, US licenced Prolia®), subject number, period, and visit (ordered by date and time within subject), as appropriate.
Data listing number and title will be unique and not being differentiated between main and transition period.
All listings will display the same number of decimals as in the source data. All raw data will be reported exactly as provided. Repeated and unscheduled assessments will be included in listing.

4.1.6 Tables

Unless otherwise specified, summaries will be provided for scheduled assessments only.

In case of scheduled assessments collected out of window, they will not be used in summaries if the deviation from scheduled window is severe, as per below defined rules. However, these data will be included in the listings and will serve for subject level safety evaluations.

Table 5 – Rules for assessments not usable in summary tables due to severe deviation from visit window

Assessment type	Criteria for inclusion of sample results in summaries and analysis
DXA Scan Assessment (collected up until 10 days after 2nd and 3rd injection as explained	If the assessment is more than 30 days prior or after the scheduled, then it is not usable in summaries nor in the analyses. In other words, the assessments will be used in the summaries and analysis only if within the below defined window:

Assessment type	Criteria for inclusion of sample results in summaries and analysis
in above section 4.2.1.1 of this SAP)	➔ Week 26: if within TP1D153 and TP1D213 (relative to the 1st injection) ➔ Week 52: if within TP1D336 and TP1D396 (relative to the 1st injection) ➔ Week 78: if within TP3D153 and TP3D213 (relative to the 3rd injection) Of note: if not falling in the above defined window, the assessment is considered severely out of schedule and considered as missing values and replaced with the MI techniques detailed in this SAP.
Pharmacodynamic (sCTX and P1NP sampling)	For Week 1 visit, result will be used in the summaries and analysis if obtained on or after day 7. For visits from Week 2 to Week 17, the result obtained on the nominal visit will be used for summaries and analysis (for AUEC calculation please refer to section 4.2.2.1 of this SAP), regardless of any time deviation from scheduled. For visits from Week 26 and subsequent visits, if the assessment is more than 3 times out of schedule, then it may not be usable in summaries nor in the analyses. In other words, the assessments will be used in the summaries and analysis only if within the below defined window: ➔ Week 1: if on or after TP1D7 ➔ Week 2: result obtained under the nominal visit regardless of any deviation from scheduled ➔ Week 4: result obtained under the nominal visit regardless of any deviation from scheduled ➔ Week 8: result obtained under the nominal visit regardless of any deviation from scheduled ➔ Week 12: result obtained under the nominal visit regardless of any deviation from scheduled ➔ Week 17: result obtained under the nominal visit regardless of any deviation from scheduled nominal visit ➔ Week 21: if within TP1D138 and TP1D162 (relative to the 1st injection)

Assessment type	Criteria for inclusion of sample results in summaries and analysis
	➔ Week 26: if within TP1D171 and TP1D195 (relative to the 1st injection) ➔ Week 52: if within TP2D171 and TP2D195 (relative to the 2nd injection) ➔ Week 78: if within TP3D171 and TP3D195 (relative to the 3rd injection)
Immunogenicity (ADAs and Nabs sampling) and serum drug concentration	In general, all results will be used in summaries and analysis under the nominal visit regardless of any time deviation from scheduled. The external laboratory will provide a comment column within the result file to indicate if the samples are to be excluded from analysis.
Any other assessment	If the assessment is more than 4-times out of schedule (in case the use of the 4-time tolerance produces an overlapping between two visits, then a 3-times out of scheduled was considered), then not usable in summaries nor in the analyses. In other words, the assessments will be used in the summaries and analysis only if within the below defined window: ➔ Week 1: if happened within TP1D5 and TP1D11 (relative to the 1st injection) ➔ Week 2: if happened within TP1D12 andTP1D18 (relative to the 1st injection) ➔ Week 4: if happened within TP1D21 andTP1D39 (relative to the 1st injection) ➔ Week 8: if happened within TP1D48 andTP1D72 (relative to the 1st injection) ➔ Week 12: if happened within TP1D78 andTP1D102 (relative to the 1st injection) ➔ Week 17: if happened within TP1D108 andTP1D132 (relative to the 1st injection) ➔ Week 21: if happened within TP1D134 andTP1D166 (relative to the 1st injection) ➔ Week 26: if happened within TP1D167 andTP1D199 (relative to the 1st injection) ➔ Week 27: if happened within TP2D5 andTP2D11 (relative to the 2nd injection)

Assessment type	Criteria for inclusion of sample results in summaries and analysis
	➔ Week 28: if happened within TP2D12 andTP2D18 (relative to the 2nd injection) ➔ Week 30: if happened within TP2D21 andTP2D39 (relative to the 2nd injection) ➔ Week 38: if happened within TP2D74 andTP2D106 (relative to the 2nd injection) ➔ Week 52: if happened within TP2D167 andTP2D199 (relative to the 2nd injection) ➔ Week 53: if happened within TP3D5 andTP3D11 (relative to the 3rd injection) ➔ Week 54: if happened within TP3D12 andTP3D18 (relative to the 3rd injection) ➔ Week 56: if happened within TP3D26 andTP3D34 (relative to the 3rd injection) ➔ Week 64: if happened within TP3D78 andTP3D102 (relative to the 3rd injection) ➔ Week 78: if happened within TP3D167 andTP3D199 (relative to the 3rd injection)

Except when considered as baseline, the repeated and unscheduled assessments will not be included in the summaries; however, if an assessment is not available at a scheduled visit or is obtained too much out of window (definition of too much out of window is provided above in Table 5 in this paragraph) while is collected in an unscheduled / end of study / early termination visit falling within the visit window for that same visit according to window above defined in Table 5, then the results obtained at unscheduled / end of study / early termination will be used in summaries under such visit; moreover if a subject is early terminating the study and the early termination visit is not falling in a visit window as per SoA, then assessments obtained at early termination visit will be presented under early termination itself.

Below cases are provided as examples:

- if a subject has vital signs collection for visit TP2 Day 15 - Week 28 performed on TP2D18 and has an unscheduled vital signs assessment on TP2D14, such unscheduled

assessment will not be used in summaries; in this case, the vital signs for TP2 Day 15 - Week 28 happened within the schedule defined in Table 5and the scheduled assessment is therefore used in summaries - if a subject has vital signs collection for visit TP2 Day 15 - Week 28 performed on TP2D20 and has an unscheduled vital signs assessment on day 14, such unscheduled assessment will be used in summaries under TP2 Day 15 - Week 28; in this case, the vital signs for TP2 Day 15 - Week 28 happened outside schedule defined in Table 5 and the scheduled assessment cannot be used in summaries

- if a subject has vital signs collection for visit TP2 Day 15 - Week 28 performed on TP2D21 and has an unscheduled vital signs assessment on TP2D14, such unscheduled assessment will be used in summaries under TP2 Day 15 - Week 28; in this case, the vital signs for TP2 Day 15 - Week 28 happened outside schedule defined in Table 5 and the scheduled assessment cannot be used in summaries; furthermore if this same subject had TP2 Day 30 - Week 30 on TP2D40 and no unscheduled / end of study / early termination between TP2D21 and TP2D39, then this subject will result having missing value at TP2 Day 30 - Week 30
- if a subject last scheduled visit was TP2 Day 30 - Week 30, then she attended early termination visit on TP2D50. Such TP2D50 assessments will be presented under early termination visit
- if a subject last scheduled visit was TP2 Day 30 - Week 30, then she attended early termination visit on TP2D88. Such TP2D88 assessments will be presented under TP2 Day 90 - Week 38

Unless specified otherwise, summary tables will be presented separately for Main (Treatment Period 1 and 2) and Transition Period.

Of note for the main and transition period analyses: unless otherwise specified, in the main period the summaries / analyses will be limited to Weeks 26 and 52, while in the transition period the analyses will be repeated in the subset of the subjects enrolled into the transition period and will

include Weeks 26, 52 and 78 for these subjects. The data cut off (main period, or main and transition) will be included on the outputs.

Within both Main and Transition Period, overall summaries will be shown for all subjects pooled together.

In general, main period tables will present results for:

- RGB-14-P
- Prolia®
- Overall (i.e., RGB-14-P and Prolia® pooled together)

In general, transition period tables will present results for:

- RGB-14-P to RGB-14-P
- Prolia® to RGB-14-P
- Prolia® to Prolia®
- Overall (i.e., the three above mentioned arms pooled together)

Changes from baseline in categorical data may be summarised using shift tables where appropriate.

In general, for variables showing multiple possible categories, these will be displayed following the within variable logic criteria, for example: adverse events severity will score from Mild and going to grow up to a maximum of Death; where such a logic criterium does not exist (example: gender, ethnicity, SOC, PT), categories will be displayed by descending frequencies based on the RGB-14-P study arm in Treatment Periods tables; in case of two categories with same count in RGB-14-P study arm in Treatment Periods tables, alphabetical order will be adopted. In the end, the order used to show categories within variables should be the same in both Treatment Periods and Transition Period tables.

4.1.7 Figures

Unless specified otherwise, figures will be presented separately for Main (Treatment Period 1 and 2) and Transition Period.

If not stated otherwise, Main and Transition Periods will be presented with the same ordinate (y) and abscissa (x) as applicable. In general, all figures will be produced in black and white; different line types can be used for each group. Additionally, some figures may also be produced in colours for scientific presentations purposes.

4.1.8 Software

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment.

4.2 Primary Endpoints Estimand Analysis

In general, if not stated otherwise the variables in this section will be listed in the FAS for the main period. This will allow to have listings on all treated subjects. When producing main period TFLs, only data included in the main period milestone data freezing scope will be printed in listing, while when producing TFLs for the whole study, all the data will be printed in listings including data pertinent to the transition period. Detailed strategy for main and transition period deliverable is in section 1 of this SAP.

4.2.1 Primary Efficacy Endpoint and Analysis

As applicable, unless otherwise stated:

- Summaries will be produced in the FAS and in the PPS in the main and transition period
- Primary treatment policy estimand will be evaluated in FAS
- Secondary principal stratum estimand will be evaluated in PPS

Multiple Imputation (MI) techniques will be proposed in this SAP; these will include concepts as missing completely at random (MCAR), missing at random (MAR) and missing non at random (MNAR) [8].

Forest plots will be produced for visual presentation of results obtained by analysing the primary efficacy endpoint with the different approaches presented in this SAP.

Forest plots will present results obtained via:

- "***Primary TPE – Regular missing data MCAR – Week 52 post-ICE2 assessments Prolia: MAR, RGB-14-P: MNAR***"

  Primary treatment policy estimand evaluated in FAS, MCAR and composite estimand strategy for ICE2, relevant for EMA submission, details in SAP section 4.2.1.2.1.1, point estimate and two sided 95% CIs will be plotted
- "***Primary TPE – Week 52 regular missing data and post-ICE2 assessments Prolia: MAR, RGB-14-P MNAR***"

  Primary treatment policy estimand evaluated in FAS, MNAR 'Under the Null' and composite estimand strategy for ICE2, relevant for FDA submission, details in SAP section 4.2.1.2.1.2
  - *non-inferiority of RGB 14-P compared to Prolia®*

    point estimate and Lower Confidence Limit (LCL) of the one sided 95% CIs will be plotted
  - *non-superiority of RGB 14-P compared to Prolia®*

    point estimate and Upper Confidence Limit (UCL) of the one sided 95% CIs will be plotted
- "***Secondary PSE – PPS, completer, not having experienced any of the two ICEs***"

  Secondary: Principal Stratum Estimand evaluated in PPS, details in SAP section 4.2.1.2.2, point estimate and two sided 95% CIs will be plotted
- "***Sensitivity TPE – Week 52 regular missing data MAR – Post-ICE2 assessments Prolia: MAR, RGB-14-P: MNAR***"

  Sensitivity for primary treatment policy estimand evaluated in FAS, missing at random (MAR) and composite estimand strategy for ICE2, relevant for EMA submission, details in SAP section 4.2.1.3.1, point estimate and two sided 95% CIs will be plotted
- "***Supplementary efficacy analysis – Regular missing data MCAR – Post-ICE assessments excluded from analysis***"

Supplementary analysis for primary treatment policy estimand evaluated in FAS, Mixed Model for Repeated Measures (MMRM) with hypothetical ICE handling strategy, details in SAP section 4.2.1.4, point estimate and two sided 95% CIs will be plotted for Week 52 results

- "***Secondary efficacy analysis – Regular missing data MCAR – Post-ICE assessments included in analysis***"
  Secondary efficacy MMRM, evaluated in both FAS and PPS, details in SAP section 4.3.1.2.2, point estimate and two sided 95% CIs will be plotted for Week 52 results

4.2.1.1 Primary Efficacy Endpoint – Definition of Endpoint

Primary efficacy endpoint consists of ***percentage of Change from Baseline (%CfB) in lumbar spine BMD (g/cm^2) at Week 52***.

Efficacy variable will be derived by data collected during the Dual Energy X-Ray Absorptiometry (DXA) scan. 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. DXA scans are planned at screening (imaging should be acquired and submitted for central independent review prior to the last week of Screening and more than one week from Randomisation), pre-dose at Week 26, Week 52 and Week 78 as per SoA (Table 10 and Table 11). For all participants bone density will be measured at the **lumbar spine, total hip** and **femoral neck** by the **BMD value**.
BMD values for the different anatomical locations will be calculated based on images by central laboratory and imported into the clinical database as external data.
As DXA scan results depend on calibration of DXA scanner used to generate the results, calibration may shift or drift, therefore calibration of scanners is monitored using phantom data (IQC). Additionally, DXA scanners are not all equivalent in calibration, so that an inter-scanner cross-calibration is also necessary for each study (XCAL). External laboratory will then provide three options for the BMD:

- BMD Measurement

- IQC Corrected BMD Measurement
- IQC and XCAL Corrected BMD

IQC and XCAL Corrected BMD will be used for the analyses; such values will be available in the external data transfer MK as per below instructions:

- **Lumbar Spine BMD (g/cm2)**: available in MK data transfer, into MKORRES variable when MKGRPID='LUMBAR SPINE' and MKLOC='LUMBAR SPINE' and MKTEST='IQC and XCAL Corrected BMD'
- **Lx Vertebra BMD (g/cm2)**: each L1, L2, L3 and L4 vertebras BMD will be available in MK data transfer, into MKORRES variable when MKGRPID='LUMBAR SPINE' and MKLOC=' Lx VERTEBRA' (where x will assume values 1, 2, 3 or 4 fo r each of the vertebras) and MKTEST='IQC and XCAL Corrected BMD'
- **Total Hip BMD (g/cm2)**: available in MK data transfer, into MKORRES variable when MKGRPID='HIP' and MKLOC='FEMUR' and MKTEST='IQC and XCAL Corrected BMD'
- **Femoral neck BMD (g/cm2)**: available in MK data transfer, into MKORRES variable when MKGRPID='HIP' and MKLOC=' FEMORAL NECK' and MKTEST='IQC and XCAL Corrected BMD'

At each anatomical location and for each efficacy assessment visit of interest (Weeks 26, 52, 78, or ET), %CfB will be computed as follows,

$$\%\text{CfB} = \frac{BMD_{WeekXX} - BMD_{Baseline}}{BMD_{Baseline}} * 100$$

where $BMD_{Baseline}$ and BMD_{WeekXX} respectively are the values of BMD assessed at baseline (last assessment before IMP administration) and at the Week of interest (Weeks 26, 52 or 78).
DXA scans collected up to 10 days after the 3rd injection will still be consider as valid assessments for the Week 52, as well DXA scans collected up to 10 days after the 2nd injection will still be considered as valid assessments for the Week 26. Example: on 15 October 2022 a patient had 3rd injection and BMD scan, but the scan was low quality and not readable, so that a new scan was requested which was done on 25 October 2022; such 25 October 2022 scan is still

to be considered as a valid Week 52 assessment. Such particular cases will all be reviewed and considered, and a decision formalized at the BDRM.

Handling of lumbar spine BMD at Week 52 will vary in the primary and secondary estimand strategy and in the sensitivity and robustness analyses and depending on EMA and FDA different approaches, detailed methods are therefore detailed in below sections 4.2.1.2, 4.2.1.3, and 4.2.1.4.

Unless otherwise stated, missing lumbar spine BMD at any other timepoint other than Week 52 and Week 78 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. Any decision about exclusion of subjects from analysis set, including cases of missing BMD baseline values, will be discussed, agreed, and documented in the BDRM prior to DB Lock.

Important note

To be noted that IQC corrections are applied to the whole pool of scans collected by a scanner machine, while XCAL is an inter-scanner correction applied upon availability of all the scans collected in the study. Both IQC and XCAL corrections are applied by the vendor.

As explained in the introduction of this SAP, there will be two DB Locks, two sets of final TFLs and two CSR for the study: the main (the first) will be including data up until Week 52, the supplemental (the second) including transition period data, i.e., up until Week 78.

Both at the Week 52 and Week 78 DB Locks, IQC and XCAL correction will be applied by the vendor.

To be noted that IQC and XCAL corrections can change between export produced for Week 52 DB Lock and final export produced Week 78 DB Lock.

This may occur in a subset of subjects whose scanners may have had shifts or drifts post Week 52, which may potentially change the IQC correction applied in the Week 52 transfer.

Moreover, the XCAL correction methodology requires that a ‘gold standard’ scanner is selected out of all scanners participating in the study for each manufacturer: Lunar and Hologic. Once the

'gold standard' scanner is identified for Lunar and Hologic, each scanner for that manufacturer is then compared to the 'gold standard' scanner and it is then determined whether an XCAL correction factor needs to be applied to the individual scanners for the manufacturer. XCAL corrections applied in the Week 52 DB Lock export may differ from the XCAL corrections applied at Week 78, which may lead to Week 52 data variations as well.

In other words, **it is expected that baseline, Week 26 and Week 52 IQC and XCAL corrected BMDs as well as vertebrae exclusions received in the Week 52 DB Lock export may differ from baseline, Week 26 and Week 52 IQC and XCAL corrected BMDs as well as vertebrae exclusions subsequently received at Week 78 DB Lock export.**

Baseline, Week 26 and Week 52 IQC and XCAL corrected BMDs received for the Week 52 DB Lock export will be used for Week 52 DB Lock activities, production of Week 52 final TFLs and production of Week 52 main CSR.

Baseline, Week 26, Week 52 and Week 78 IQC and XCAL corrected BMDs received for the Week 78 DB Lock export will be used for Week 78 DB Lock activities, production of Week 78 final TFLs and production of Week 78 transition CSR.

4.2.1.2 Primary Efficacy Endpoint – Main Analytical Approach

By-subject listing of BMD data will be provided.

Visit-wise summaries of BMD data, CfB and %CfB will be provided for the treatment arms in main and transition period. Summaries of missing primary efficacy endpoint will be provided for Week 52 and Week 78.

Missing total hip and femoral neck BMD will not be imputed and will thus result in missing %CfB.

4.2.1.2.1 Primary Efficacy Endpoint – Primary estimand

Table 2 summarises the primary analysis will be conducted to evaluate the primary endpoint of the study using a Treatment Policy Estimand. More in details, a model of Analysis of Covariance (ANCOVA) will be implemented to estimate the difference of means between the test and reference arms in percentage change from baseline of BMD in lumbar spine at Week 52. The

observed %CfB in lumbar spine BMD at Week 52 (as defined in Section 4.2.1.1) will be the dependent variable while the followings will be used as covariates:

- Treatment Arm (RGB-14-P and US-licenced Prolia®, as planned (randomised) treatment)
- Stratification factors at randomisation:
  - Previous use of bisphosphonates (yes/no)
  - Geographical region (Europe, US)
- Baseline BMD value in lumbar spine
- Machine type (as per DXA scan external data transfer)
- Machine type * Baseline BMD value interaction

As result from ANCOVA model, the effect $\hat{\delta}_{TPE}$ of the binary variable Treatment Arm will be estimated as regression coefficients. Wald's two-sided 95% Confidence Interval (CI) will be derived for the parameter estimate.

Handling of intercurrent events

ICE 1, the first and/or the second dose of randomised IMP is not administered, will be handled under treatment policy strategy: all obtained data points will be included in the analysis, in line with the ITT principle.
ICE 2 will consist of the participant receiving other medication alongside the IMP, which affects the primary variable, i.e., prohibited therapies as per SAP section 6.2.8. Composite variable strategy will be applied; Intercurrent event is considered to be informative about the outcome, so that the responses obtained after ICE occurrence will be imputed under the null hypothesis.
Details about strategy implementation for EMA and FDA submissions are outlined here below.
Descriptive analysis of the number, proportion and timing of intercurrent events (ICEs) will be presented.

4.2.1.2.1.1 EMA submission

To test the hypothesis of equivalence, the $\hat{\delta}_{TPE}$ 95% CIs, as obtained by the ANCOVA model described in section 4.2.1.2.1, will be studied. If the LCL of the two-sided 95% CI around $\hat{\delta}_{TPE}$ will be greater than [redacted] and the UCL will be less than [redacted], the null hypothesis will be rejected.
Missing data without experiencing ICE2 will be assumed to be MCAR and will not be imputed.
Assessments of the primary endpoints observed after occurrence of ICE2 will be disregarded, i.e., artificially set as missing, and will be replaced with MI techniques.
Different assumptions will be made for handling of ICE2 in each of the two arms. Under Prolia® group, data artificially set as missing after ICE2 occurrence will be assumed to be MAR and imputed assuming they would have behaved like subjects in the same arm had they not taken prohibited medication. Under the RGB-14-P group, Week 52 data artificially set as missing after ICE2 occurrence will be imputed using MNAR method 'Under the Null': after ICE2 primary efficacy data are assumed to worsen from "MAR" by an amount of equivalence margin "delta" [9][10]. The [redacted] will be used as the "delta" for the ICE2 in the RGB-14-P group [11].
MI will be performed through SAS PROC MI, variables used to impute Week 52 missing values will be the dependent variables from ANCOVA model defined at section 4.2.1.2.1; additionally, Week 26 data will be used as well in the SAS PROC MI as a post-randomization predictive variable; in that contest the post-ICE2 Week 26 BMD will be imputed as well within the SAS PROC MI itself, with MAR approach for both the treatment arms.
Below steps will be followed (note: the steps below will be executed on a copy of the BMD %CfB column variable, while the original will be maintained as well):

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

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

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

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

Step 5) From the dataset created at Steps 3 and 4, only data imputed because of ICE2 occurrence will be retained, while data that were originally missing will be reverted back as missing. The two resulting datasets will then be compiled in a unique dataset

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

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

As a title of example, a SAS code to implement the steps is provided in section 6.4.2.

As sensitivity analysis, missing data will be imputed in accordance with techniques proposed by Jakobsen et al (2017) [4], which will be considered as described in section 4.2.1.3: if the proportion of non-complete cases is below 5%, sensitivity analysis will be not conducted.

4.2.1.2.1.2 FDA submission

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 MI method. Specifically, for the first test, i.e., test of non-inferiority, missing week 52 values for the RGB-14-P group will be imputed under the corresponding CCI CCI; for the second test, i.e., test of non-superiority, missing week 52 values for the RGB-14-P group will be imputed under the corresponding CCI CCI. 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 randomised subjects with baseline BMD will be included in the analysis.

In other words, to test the hypothesis of equivalence, two one-sided tests at alpha=0.05 will be conducted with the following null hypotheses of non-inferiority and non-superiority:

- *Non inferiority of RGB 14-P compared to Prolia®* H_0: $\delta_{TPE} \leq$ CCI
- *Non superiority of RGB 14-P compared to Prolia®* H_0: $\delta_{TPE} \geq$ CCI

Equivalence with respect to the primary efficacy endpoint is demonstrated if both null hypotheses are rejected.

For FDA submission, missing primary efficacy post baseline data will be imputed with MI techniques. Furthermore, assessments of the primary endpoints observed after occurrence of ICE2 will be disregarded, i.e., artificially set as missing, and will be imputed with same MI techniques as applied to regular missing data.

Prolia® group subjects with missing values (originally or post-ICE2 assessments) will be assumed to be MAR and imputed assuming they would have behaved like subjects in the same arm had they not have a missing value or taken prohibited medication.

RGB-14-P group subjects' with missing Week 52 values (originally or post-ICE2 assessments) will be imputed using MNAR method 'Under the Null': missing primary efficacy data are assumed to worsen from "MAR" by an amount of equivalence margin "delta" [9][10]. The CCI [redacted] will be used as the "delta" for the RGB-14-P group [11].

MI will be performed through SAS PROC MI, variables used to impute Week 52 missing values will be the dependent variables from ANCOVA model defined at section 4.2.1.2.1; additionally, Week 26 data will be used as well in the SAS PROC MI as a post-randomization predictive variable; in that contest the missing Week 26 (originally or post-ICE2 assessments), will be imputed as well within the SAS PROC MI itself, with MAR approach for both the treatment arms.

Below steps will be followed (note: the steps below will be executed on a copy of the BMD %CfB column variable, while the original will be maintained as well):

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

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

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

Step (4) In the RGB-14-P dataset created in Step 2, Week 52 %CfB missing or assessed after ICE2 occurrence will be imputed as MNAR. SAS PROC MI will be executed with FCS method, 50 complete datasets will be created, seed 252679 will be used, variables used to impute missing values will be the stratification factors (previous use of bisphosphonates and geographical region), baseline BMD, machine type and Week 26 lumbar spine BMD %CfB. MNAR statement

will be used including ADJUST option with SHIFT as sub option, allowing a shift to be applied to the Week 52 values imputed. Shift will be of CCI when testing non-inferiority and CCI when testing non-superiority

Step (5) MI datasets resulting from Steps 3 and 4 will be compiled in a unique dataset, with Prolia® having been imputed under MAR and RGB-14-P under MNAR assumption

Step (6) The primary efficacy ANCOVA model as defined at section 4.2.1.2.1 will be executed in the dataset obtained in Step 5 by imputation, so to get results from each of the 50 complete datasets

Step (7) Estimates obtained in Step 6 will then be combined through SAS MIANALYZE, alpha will be set at 10%. Combined estimation of the difference RGB 14-P – Prolia will be examined together with the corresponding one-sided 95% CI:

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

non-inferiority will be claimed if the LCL will be greater than CCI

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

non-superiority will be claimed if the UCL will be less than CCI.

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 at the 5% level each; considering the use of MI, all randomised subjects with a baseline measurement will be included in the analysis.

As a title of example, a SAS code to implement the steps is provided in section 6.4.3.

4.2.1.2.2 Primary Efficacy Endpoint – Secondary estimand

As described in Table 2, the secondary analysis will be conducted to evaluate the primary endpoint of the study using a Principal Stratum Estimand (PSE).
PSE strategy relates to a target population of interest, taken as the principal stratum, in which both ICEs would not occur. The clinical question of interest relates to the treatment effect only

within the principal stratum. PSE is based on potential ICEs occurrence, i.e., subjects who would have ICE occurrence if assigned to either treatment arm.

Let U denote the principal stratum defined by the joint potential PPSC (Per-Protocol and Completer) and PSE (i.e., not having experienced the two ICEs as defined in Table 1) status had a subject been assigned to RGB-14-P and US-licenced Prolia®, $U = \{S_1, S_0\} = \{ss, s\bar{s}, \bar{s}s, \bar{s}\bar{s}\}$.

There are four principal strata:

- "Always PPSC & PSE" $(U = ss)$:$(U = ss)$: Participant who would comply with study (i.e., be PPSC & PSE) under both RGB-14-P and US-licenced Prolia®.
- "PPSC & PSE with RGB-14-P only" $(U = s\bar{s})$:$(U = s\bar{s})$: Participant who would be PPSC & PSE if assigned to RGB-14-P, but would not if assigned to US-licenced Prolia®.
- "PPSC & PSE with US-licenced Prolia® only" $(U = \bar{s}s)$:$(U = \bar{s}s)$: Participant who would be PPSC & PSE if assigned to US-licenced Prolia®, but would not if assigned to RGB-14-P.
- "Never PPSC & PSE" $(U = \bar{s}\bar{s})$:$(U = \bar{s}\bar{s})$: Participant who would not be PPSC nor PSE regardless of the treatment group being assigned to.

Under the assumptions of Stable Unit Treatment Values Assumption (SUTVA) and random assignment of the current study, the Survivor Average Causal Effect (SACE) estimand of the difference of means between the RGB-14-P and US-licenced Prolia® arms in percentage change from baseline of BMD is composed of two parts, as follows

$$\delta_{SACE} = \delta_{PST} + \boldsymbol{BIAS} = \delta_{PST} + \frac{\boldsymbol{\pi_{\bar{s}s}}}{\boldsymbol{p_0}}\boldsymbol{\beta_0} - \frac{\boldsymbol{p_1 - p_0 + \pi_{\bar{s}s}}}{\boldsymbol{p_1}}\boldsymbol{\beta_1},$$

where:

- δ_{PST}: principal stratum estimate of the effect (difference) in mean (from ANCOVA).
- $\pi_{\bar{s}s}$: marginal proportion of PPSC & PSE with US-licenced Prolia® only
- p_0: proportion of being observed PPSC & PSE subjects in the US-licenced Prolia®
- p_1: proportion of being observed PPSC & PSE subjects in the RGB-14-P

- β_0: is the difference in average potential outcome under US-licenced Prolia® arm between the stratum "PPSC & PSE with US-licenced Prolia® only" and the stratum "always PPSC & PSE"
- β_1: is the difference in average potential outcome under RGB-14-P arm between the stratum "PPSC & PSE with RGB-14-P only" and the stratum "always PPSC & PSE"

As for the secondary estimand analysis for this bioequivalence study, no deviations are expected in the two arms from the stratum of from "always PPSC & PSE", therefore $\beta_0 = 0$ and $\beta_1 = 0$ will be considered. In other words, $\delta_{SACE} = \delta_{PST}$ is assumed for secondary estimand analysis. Parameters β_0 and β_1 , as well as $\pi_{\bar{s}s}$, will be made to vary as part of the sensitivity tipping point as described in section 4.2.1.3.3 of this SAP.

A model of Analysis of Covariance (ANCOVA) will be used to estimate δ_{PST}: the observed %CfB in lumbar spine BMD at Week 52 (as defined in Section 4.2.1.1) will be the dependent variable while the followings will be model covariates:

- Treatment Arm (RGB-14-P and US-licenced Prolia®, as planned treatment)
- Stratification factors for randomisation:
  - Previous use of bisphosphonates (yes/no)
  - Geographical region (Europe, US)
- Baseline BMD value in lumbar spine
- Machine type (as per DXA scan external data transfer)
- Machine type * Baseline BMD value interaction

As result from ANCOVA model, the estimated effect $\hat{\delta}_{PST}$ of the binary variable treatment arm will be obtained as regression coefficients. Wald's two-sided 95% CI will be derived for the parameter estimate.

As a title of example, a SAS code is provided in section 6.4.1.

To test the hypothesis of equivalence, the $\hat{\delta}_{PST}$ 95% CIs will be studied. If the LCL of the 95% CIs around $\hat{\delta}_{PSE}$ will be greater than [redacted] and the UCL will be less than [redacted] the null hypothesis will be rejected.

If the proportion of non-complete cases in subjects PPS & PSE is higher than 5%, 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. Approach for MI will be similar to one used for primary efficacy primary estimand for FDA submission, which is treated in section 4.2.1.2.1.2.

4.2.1.3 Primary Efficacy Endpoint – Sensitivity Analyses

4.2.1.3.1 Primary Efficacy Endpoint – Primary estimand sensitivity analysis for EMA submission

For EMA submission, missing primary efficacy post baseline data will be imputed as a sensitivity estimation. As sensitivity analysis, missing data will be imputed in accordance with techniques proposed by Jakobsen et al (2017) [4]: if the proportion of non-complete cases is below 5%, sensitivity analysis will be not conducted.

Missing data will be assumed to be MAR and imputed using fully conditional specification (FCS) method via SAS PROC MI. Additionally, likewise for the primary endpoint primary estimand analysis as outlined in section 4.2.1.2.1.1, assessments of the primary endpoints observed after occurrence of ICE2 will be disregarded, i.e., artificially set as missing, and will be replaced with MI techniques. Different assumptions will be made for handling of ICE2 in each of the two arms. Under Prolia® group, data artificially set as missing after ICE2 occurrence will be assumed to be MAR and imputed assuming they would have behaved like subjects in the same arm had they not taken prohibited medication. Under the RGB-14-P group, Week 52 data artificially set as missing after ICE2 occurrence will be imputed using MNAR method 'Under the Null': after ICE2 primary efficacy data are assumed to worsen from "MAR" by an amount of equivalence margin

"delta" [9][10]. The equivalence margin of [redacted] will be used as the "delta" for the RGB-14-P group [11].

MI will be performed through SAS PROC MI, variables used to impute Week 52 missing values will be the dependent variables from ANCOVA model defined at section 4.2.1.2.1; additionally, Week 26 data will be used as well in the SAS PROC MI as a post-randomization predictive variable; in that contest the missing Week 26 (originally or post-ICE2 assessments) will be imputed as well within the SAS PROC MI itself, with MAR approach for both the treatment arms.

Below steps will be followed (note: the steps below will be executed on a copy of the BMD %CfB column variable, while the original will be maintained as well):

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

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

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

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

ADJUST option with SHIFT and ADJUSTOBS as sub options, allowing a shift of -1.45 to be applied to only the value imputed after occurrence of ICE2.

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

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

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

As a title of example, a SAS code to implement the steps is provided in section 0.

4.2.1.3.2 Primary Efficacy Endpoint – Primary estimand sensitivity tipping point for FDA submission

For FDA submission, robustness of the main estimator will be assessed by using two-dimensional tipping point analyses allowing assumptions about missing Week 52 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. Again, assessments of the primary endpoints observed after occurrence of ICE2 will be disregarded, i.e., artificially set as missing, and will be imputed in the tipping point analysis with same MI techniques as applied to regular missing data.

The analysis finds a (tipping) point in this spectrum of assumptions, at which conclusions change from being favorable to the experimental treatment to being unfavorable. After such a tipping point is determined, clinical judgment can be applied as to the plausibility of the assumptions underlying this tipping point. Tipping point analysis is a method of exploring the influence of missingness on the overall conclusion of the treatment difference by shifting imputed missing values in the test group towards the reference group until the study results are reversed. Tipping point is evaluated based on a series of shift parameters.

Different assumptions will be made for missing values (and post-ICE2 assessments) in each of the two arms. SAS PROC MI will be utilised with MNAR statement including ADJUST option with SHIFT as sub option to allow the Week 52 outcomes in the two treatment arms to vary independently.

To stress both non-inferiority and non-superiority null hypotheses, a broad range of shifts will be applied to the two arms, so to obtain a quasi-quantitative 'delta' variation.

For MI procedure, analysis of MI data and results combination for each imputation, similar techniques will be used as presented in section 4.2.1.2.1.2, details will follow in the below.

Tipping point analysis will be executed following two approaches. If equivalence is established in the two approaches, it will be concluded that the MI method used for handling missing (and post-ICE2 assessments) is not impacting the study results interpretation; however, if equivalence is not consistently established with both the two approaches, then the tipping points reversing study conclusions will be evaluated from medical point of view to determine if such scenarios are clinically plausible.

Under both approaches, MI will be performed through SAS PROC MI. Variables used to impute Week 52 missing values will be the dependent variables from ANCOVA model defined at section 4.2.1.2.1; additionally, Week 26 data will be used as well in the SAS PROC MI as a post-randomization predictive variable; in that contest the missing Week 26 (originally or post-ICE2 assessments) will be imputed as well within the SAS PROC MI itself, with MAR approach for both the treatment arms.

Tipping point analysis approach 1

Week 52 Prolia® MI under MAR assumption (i.e., shift = 0), RGB 14-P MI assumed MNAR (i.e., shifts under the null hypothesis).

MAR assumption applied to Prolia® (i.e., shift = 0), while in RGB 14-P arm shifts will be applied ranging from 'delta' (CCI when testing non-inferiority, CCI when testing non-

superiority) to approximately 5 times delta (-7.45 when testing non-inferiority, 7.45 when testing non-superiority).

Below steps will be followed (note: the steps below will be executed on a copy of the BMD %CfB column variable, while the original will be maintained as well):

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

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

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

Step 4) In the RGB-14-P dataset created in Step 2, Week 52 %CfB missing or assessed after ICE2 occurrence will be imputed as MNAR. SAS PROC MI will be executed with FCS method, 50 complete datasets for each applied shift will be created, seed 252679 will be used, variables used to impute missing values will be the stratification factors (previous use of bisphosphonates and geographical region), baseline BMD, machine type and Week 26 lumbar spine BMD %CfB. MNAR statement will be used including ADJUST option with SHIFT as sub option, allowing a shift to be applied to the Week 52 values imputed. Different shifts will be applied as part of this tipping point analysis: shifts will vary from CCI [redacted] to -7.45 when testing non-inferiority, from CCI [redacted] to 7.45 when testing non-superiority, by incremental value of 1.

Step 5) MI datasets resulting from Steps 3 and 4 will be compiled in a unique dataset for each shift applied.

Step 6) Separately for each RGB-14-P shift level, the primary efficacy ANCOVA model as defined at section 4.2.1.2.1 will be executed by imputation on complete dataset obtained from Step 5.

Step 7) Estimates from the Step 6 will then be combined through SAS MIANALYZE, by each RGB-14-P shift level, alpha will be set at 10%. Combined estimation of the difference RGB 14-P – Prolia will be examined together with the corresponding one-sided 95% CI:

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

non-inferiority will be confirmed if the LCL will be greater than CCI

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

non-superiority will be confirmed if the UCL will be less than CCI

Step 8) If non-inferiority (non-superiority) is confirmed under all shifts, the procedure will end, and it will be concluded that approach 1 suggests that the method used for MI of missing (and post-ICE2 assessments) is not impacting the results interpretation;

If non-inferiority (non-superiority) is not confirmed under all shifts, then the procedure will continue to Step 9 below

Step 9) If the non-inferiority (non-superiority) conclusion is reverted, then the 'area' thresholds where such conversion is observed, which will have extent of 1, will be further examined in deeper detail; Steps 3 to 7 will be repeated; in Step 4 RGB 14-shifts will be made to vary from lower to upper 'area' thresholds by incremental value of 0.1; this will allow to identify a stricter 'area' threshold where study conclusion are reversed; such stricter 'area' will have extent of 0.1 and will be investigated in deeper detail as per below Step 10

Step 10) Steps 3 to 7 will be repeated again; in Step 4 RGB 14-shifts will be made to vary within the stricter 'area' thresholds identified in above Step 9; shifts will be made to vary from lower to upper stricter 'area' thresholds by incremental value of

0.01; this will allow to identify the tipping point reversing the study conclusion with a detail of two decimal places

Results obtained while running the approach 1 will be tabulated, including the shift applied to the RGB 14-P, the point estimate obtained for the primary endpoint together with the two-sided 90% Cis and the standard error. When testing non-inferiority, observed LCL for the different RGB 14-P will be plotted, observed UCL will be plotted when testing non-inferiority. A forest plot will be present as well: point estimate and 90% Cis will be plotted for all the different RGB 14-P shifts under the non-inferiority and non-superiority tests.

Execution of above-described approach 1 will be supported by SAS macro available at section 6.4.5 of this SAP. Such macro was developed based on an example available from SAS user guide [20]. SAP section 6.4.5 also provides sample SAS code for the required plots.

Tipping point analysis approach 2

Week 52 Prolia® and RGB 14-P MI assumed MNAR (i.e., shifts under the null hypothesis).

MNAR shifts will be applied to both Prolia® and RGB 14-P arm shifts ranging from 'delta' to approximately 5 times delta.

When testing non-inferiority, shifts in the range from CCI to 7.45 will be applied to Prolia® while shifts in the range from -7.45 to CCI will be applied to RGB 14-P.
Conversely, when testing non-superiority, shifts in the range from -7.45 to CCI will be applied to Prolia® while shifts in the range from CCI to 7.45 will be applied to RGB 14-P.Below steps will be followed (note: the steps below will be executed on a copy of the BMD %CfB column variable, while the original will be maintained as well):

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

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

Step 3) In the Prolia® dataset created in Step 2, Week 52 %CfB missing or assessed after ICE2 occurrence will be imputed as MNAR. SAS PROC MI will be executed with FCS method, 50 complete datasets will be created, seed 252679 will be used, variables used to impute missing values will be the stratification factors (previous use of bisphosphonates and geographical region), baseline BMD, machine type and Week 26 lumbar spine BMD %CfB. MNAR statement will be used including ADJUST option with SHIFT as sub option, allowing a shift to be applied to the Week 52 values imputed. Different shifts will be applied as part of this tipping point analysis: shifts will vary from CCI to 7.45 when testing non-inferiority, from -7.45 to CCI when testing non-superiority, by incremental value of 1.

Step 4) In the RGB-14-P dataset created in Step 2, Week 52 %CfB missing or assessed after ICE2 occurrence will be imputed as MNAR. SAS PROC MI will be executed with FCS method, 50 complete datasets will be created, seed 252679 will be used, variables used to impute missing values will be the stratification factors (previous use of bisphosphonates and geographical region), baseline BMD, machine type and Week 26 lumbar spine BMD %CfB. MNAR statement will be used including ADJUST option with SHIFT as sub option, allowing a shift to be applied to the Week 52 values imputed. Different shifts will be applied as part of this tipping point analysis: shifts will vary from -7.45 to CCI when testing non-inferiority, from CCI to 7.45 when testing non-superiority, by incremental value of 1.

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

Step 6) Separately for each combination of Prolia® and RGB-14-P shift level, the primary efficacy ANCOVA model as defined at section 4.2.1.2.1 will be executed by imputation on complete dataset obtained from Step 5

Step 7) Estimates from the Step 6 will then be combined through SAS MIANALYZE, by each RGB-14-P shift level, alpha will be set at 10%. Combined estimation of the

difference RGB 14-P – Prolia will be examined together with the corresponding one-sided 95% CI:

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

non-inferiority will be confirmed if the LCL will be greater than CCI

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

non-superiority will be confirmed if the UCL will be less than CCI

Step 8) If non-inferiority (non-superiority) is confirmed under all shift combinations, the procedure will end, and it will be concluded that approach 2 suggests that the method used for MI of missing (and post-ICE2 assessments) is not impacting the results interpretation

If non-inferiority (non-superiority) is not confirmed under all shifts, then the procedure will continue to Step 9 below

Step 9) If the non-inferiority (non-superiority) conclusion is reverted, then the 'area(s)' thresholds where such conversion is observed, which will have extent of 1, will be further examined in deeper detail; Steps 3 to 7 will be repeated in each area where the conversion is observed; in Steps 3 and 4, within each identified 'area', Prolia® and RGB 14-shifts will be made to vary from lower to upper 'area' thresholds by incremental value of 0.1; this will allow to identify stricter 'area(s)' threshold where study conclusion are reversed; such stricter 'area(s)' will have extent of 0.1 and will be investigated in deeper detail as per below Step 10

Step 10) Steps 3 to 7 will be repeated again; in Steps 3 and 4, within each identified stricter 'area', Prolia® and RGB 14-P shifts will be made to vary within the stricter 'area' thresholds identified in above Step 9; shifts will be made to vary from lower to upper stricter 'area' thresholds by incremental value of 0.01; this will allow to identify the tipping points reversing the study conclusion with a detail of two decimal places

Results obtained while running the approach 2 will be tabulated, including the shift applied to Prolia® and RGB 14-P, the point estimate obtained for the primary endpoint together with the two-sided 90% CIs and the standard error. For different combinations of Prolia® and RGB 14-P shifts:

- observed LCL will be plotted when testing non-inferiority, UCL when testing non-superiority
- forest plots will also be present, plotting point estimate and 90% CIs under the non-inferiority and non-superiority tests

Execution of above-described approach 2 will be supported by SAS macro available at section 6.4.6 of this SAP. Such macro was developed based on an example available from SAS user guide [20]. SAP section 6.4.6 also provides sample SAS code for the required plots.

4.2.1.3.3 Primary Efficacy Endpoint – Secondary estimand sensitivity tipping point analysis

Due to the nature of study design, robustness of the estimator will be assessed by implementing in a Causal Inference framework, as proposed by Lou et al. [5]. More in detail, principal stratification approach will be followed.

The BIAS component of the δ_{SACE} formula will be studied, please refer to formula and terminology presented in section 4.2.1.2.2 of this SAP.

A tipping point sensitivity analysis will be conducted to evaluate the robustness of the conclusion based on the observed principal stratum [PST] estimator under different scenarios, by varying the values of β_0, β_1 and $\pi_{\bar{s}s}$ within clinically meaningful ranges. Boundaries for the range of $\pi_{\bar{s}s}$ can be easily derived as

$\pi_{\bar{s}s} \in [\max(0, p_0 - p_1), \min(p_0, 1 - p_1)]$.

The proportion of PST with US-licenced Prolia® only is bounded, but the selection effects (β_0, β_1) are not.

The robustness analysis will be conducted, below steps will be followed:

Step 1) Compute $\hat{p}_0$ and $\hat{p}_1$ and compute the $\hat{\delta}_p = \hat{p}_1 - \hat{p}_0$ and derive the two-sided 90% confidence interval of $\hat{\delta}_p$ using Yates's continuity correction. If the 90% CI is included in the specific equivalence margin, tipping point analysis can be performed. For this study, the specific equivalence margin for the difference of proportion of PSE subjects is set as ± 15%

Step 2) Estimate $\hat{\delta}_{PST}$ and Wald's 95% CI by ANCOVA model (δ_{PST} as estimated by the secondary estimand analysis described in section 4.2.1.2.2 of this SAP)

Step 3) Compute the boundaries for $\pi_{\bar{s}s}$ as previously defined and identify a few cut point inside the range to perform tipping point analysis (for example if the range of $\pi_{\bar{s}s}$ is between 0 and 15%, it is suggested to cover the interval with 0%, 5%, 10% and 15%). Furthermore, derive $\hat{\pi}_{s\bar{s}}$ as:

$$\pi_{s\bar{s}} = \hat{p}_1 - \hat{p}_0 + \pi_{\bar{s}s}$$

Step 4) For each value of $\pi_{\bar{s}s}$,a clinical meaningful range is set for β_0 and β_1 (for example, between ±35%)

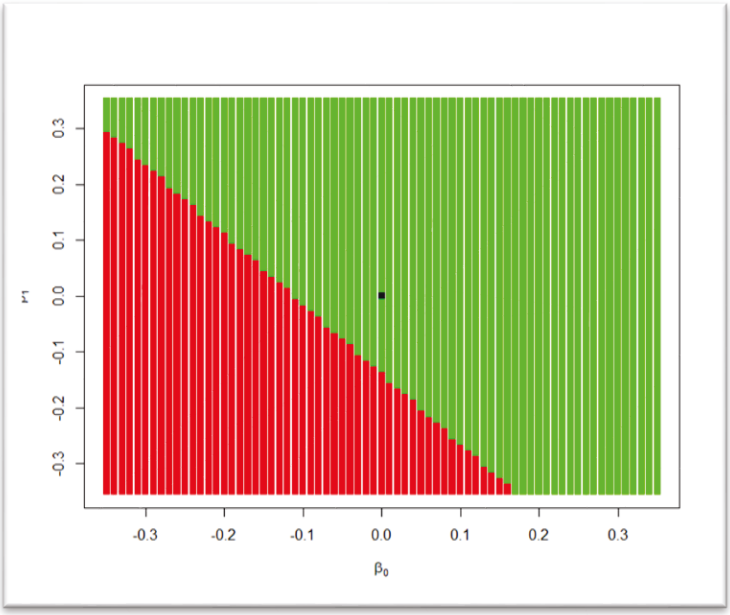
Step 5) Compute $\hat{\delta}_{SACE}$ as defined below with its 95% CI: because the sensitivity parameters are considered as "fixed," the 90% CI for an estimator of the SACE can simply be constructed by shifting the CI of the observed δ_{PST} (as estimated by the secondary estimand analysis described in section 4.2.1.2.2 of this SAP) by the BIAS

Step 6) Figure 3 shows an example of tipping point plot. A plot will be produced for each value of a series that cover the whole $\pi_{\bar{s}s}$. Horizontal and vertical axes respectively represent values for β_0 and β_1. Considering the value of $\pi_{\bar{s}s}$ and for each value of β_0 and β_1, $\hat{\delta}_{SACE}$ and its 95% are derived. If the LCL for the set of β_0, β_1 and $\hat{\pi}_{\bar{s}s}$ is greater than CCI and UCL is less than CCI the point is plotted as green, while red otherwise. The black point is $\hat{\delta}_{PST}$ where the BIAS quantity is zero due to $\beta_0 = \beta_1 = 0$

Step 7) If most of the multiple plots, which cover the range of variation of $\pi_{\bar{s}s}$, will not show large red areas close to the PST estimate black point, the equivalence conclusion would be considered robust. The equivalence conclusion reverses only if the selection effects under RGB 14-P and US licenced Prolia® are very unbalanced (i.e., if the absolute value of $\beta_0 - \beta_1$ is large). This will happen if RGB 14-P and US licenced Prolia® have very different safety and efficacy profiles

Step 8) The associated green/red value related to any $\hat{\delta}_{SACE}$ values will be listed and quantitative summaries will be provided

Figure 3 – Example of Tipping Point Plot



Such robustness analysis may be executed in software R [22].

4.2.1.4 Primary Efficacy Endpoint – Supplementary Analyses

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

Data points captured after the ICE will be left out from the FAS analysis. The same ICEs will be applied as for the primary and secondary estimands.
Primary endpoint will be analysed by using MMRM with the following factors:.

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

Unstructured covariance matrix will be used. In case of convergence issues, alternative structures will be considered in the following order: Autoregressive(1), Compound Symmetry, Toeplitz; until convergence is met.
Missing data will be assumed to be MCAR and will not be imputed.
As a title of example, a SAS code to implement the steps is provided in section 6.4.7.

4.2.2 Primary Pharmacodynamic Endpoint and Analysis

Of note: pharmacodynamic results are received from external vendor laboratory; in some instances, sCTX results were received with the two test codes ZCTXG and ZCTX1; in these instances, based on instructions received from laboratory, the results received under code ZCTXG is to be considered as latest and more accurate and used for summaries, analysis and any derivation detailed in this SAP; both results obtained under ZCTXG and ZCTX1 will be displayed in the data listings, with a clear identification key for results received under code ZCTXG and under code ZCTX1.

4.2.2.1 Primary Pharmacodynamic Endpoint – Definition of Endpoint

AUEC of %CfB sCTX0-m6 until Week 26 is the primary pharmacodynamic variable.

sCTX PD markers will be measured and compared as specified at the endpoint. Blood samples will be collected for measurement of serum concentrations of sCTX as per SoA (Table 10 and Table 11). Baseline is defined as the concentration values of sCTX derived by serum sampling collected pre-dose at Day 1 Week 0.

As sCTX values are expected to decrease over time following injection, the CfB will be derived and interpreted as a reduction from baseline. %CfB in serum sCTX will then be computed as follows,

$$\%\text{CfB sCTX} = \frac{sCTX_{baseline} - sCTX_{timepoint}}{sCTX_{baseline}} * 100$$

where $sCTX_{\text{baseline}}$ and $sCTX_{\text{timepoint}}$ respectively are concentration values at baseline (including pre-dose at Day 1, Week 0) and at post-baseline timepoint.

The %CfB AUEC after first dose until Week 26 in $sCTX_{0\text{-m6}}$ will be estimated as key PD parameter for the primary endpoint.

The AUEC of %CfB sCTX(0-m6) will be calculated as the area under/over 0 after the first dose administration (Day 1 Week 0) until week 26.

AUEC of %CfB sCTX(0-m6) is calculated as follows:

$$AUEC(\text{0-m6}) = \int_0^{week\ 26} E(t)dt$$

The trapezoidal method will be employed for all trapezoids arising from %CfB sCTX. The area under the %CfB-time curve will be divided into a series of trapezoids, each bounded by two consecutive time points and corresponding %CfB sCTX values.

For each trapezoid, the area will be calculated via the formula:

Piecewise area = (d2 – d1) * (C1 + C2) / 2

where d1 and d2 are the time points at the boundaries of the trapezoid and C1 and C2 are the corresponding %CfB sCTX values at those time points. The AUEC value is obtained by summing the areas of all the trapezoids between the initial time point (day1) and the final time

point (Week 26) Example for %CfB AUEC derivation is provided in appendix section 6.4.8;actual days will be used for the calculation of the AUEC.

4.2.2.2 Primary Pharmacodynamic Endpoint – Main Analytical Approach

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 presented as BLQ in listing. In summary tables and graphically representation, including derivation of AUEC, values BLQ will be imputed as LLOQ. The individual serum concentration of sCTX, %CfB and AUEC of %CfB will be listed and summarised in tabular and graphical format by treatment group at each planned sampling time using descriptive statistics.

Analysis will be performed on the PDS population.

To evaluate the %CfB AUEC sCTX0-m6 (required as primary endpoint for EMA and secondary for FDA), the treatment comparison will be made using the ANCOVA with natural log-transformed AUEC data as the dependent variable while the followings will be model covariates:

- Treatment Arm.
- Stratification factors for randomisation:
    - Previous use of bisphosphonates (yes/no)
    - Geographical region (Europe, US)

- Log of baseline sCTX

LS means for %CfB AUEC sCTX0-m6 will be back transformed to derive geometric means and presented with the corresponding LS GMR with their corresponding 95% CIs. Geometric LS mean ratios will be derived by back transforming the LS mean difference between RGB-14-P and Prolia® (RGB-14-P - Prolia®) and presented as ratio (GMR). Back transformed LS mean and GMR will be presented as percentages, as well as the corresponding CIs. Delta method was applied to back transform geometric mean standard error used for the computation of corresponding 95% CIs. As an example, SAS code is provided in section 6.4.9.
Pharmacodynamic equivalence will be concluded if the 95% CI of the treatment GMR is contained within the 80% to 125% equivalence margin.

4.2.2.3 Primary Pharmacodynamic Endpoint – Sensitivity Analyses

Not Applicable.

4.2.2.4 Primary Pharmacodynamic Endpoint – Supplementary Analyses

Not Applicable.

4.3 Secondary Endpoints and Analysis

4.3.1 Secondary Efficacy Endpoints

Secondary efficacy endpoints are listed in section 1.1, Table 1.
As applicable, unless otherwise stated, secondary efficacy analyses will be executed in FAS and PPS in the main and transition period.

4.3.1.1 Secondary Efficacy – Definition of Endpoint(s)

4.3.1.1.1 %CfB in total hip BMD at Weeks 26, 52 and 78

As derivations and data handling are very similar to those necessary for the primary endpoint, this secondary endpoint was described in section 4.2.1.1; please refer to that section for detailed instructions.

4.3.1.1.2 %CfB in lumbar spine BMD at Weeks 26 and 78

As derivations and data handling are very similar to those necessary for the primary endpoint, this secondary endpoint was described in section 4.2.1.1; please refer to that section for detailed instructions.

4.3.1.1.3 %CfB in femoral neck BMD at Weeks 26, 52 and 78

As derivations and data handling are very similar to those necessary for the primary endpoint, this secondary endpoint was described in section 4.2.1.1; please refer to that section for detailed instructions.

4.3.1.1.4 Vertebral fragility fracture incidence

Information on vertebral fractures will be centrally collected through the evaluation of lateral thoraco-lumbar spine X-ray planned at screening, Weeks 52 and 78, as per SoA (Table 10 and Table 11). For central assessment of vertebral fractures by lateral spine X-ray, the Genant visual semiquantitative grading scale will be used [12], Genant scores range 0 – 3 for presence and severity of vertebral fractures (0 = normal, 1 = mild, 2 = moderate, 3 = severe). A value of 0 will be interpreted as no vertebral fracture, while values higher than 0 will be interpreted as presence of a vertebral fracture with severity indicated by the score itself. Genant score is received into the MO X-ray external data transfer, when variable MOTESTCD = ANASCORE the associated MOORRES contains the Genant score. Any vertebral fracture emerging or worsening in the Genant score on or after first IMP injection, fracture will be considered for this endpoint.

Furthermore, collected AEs will be scrutinised by the Medical Monitor to flag vertebral fracture events. A reconciliation should happen between vertebral fracture events as flagged into the X-ray external data transfer and events logged as AEs into the EDC, as any fracture (symptomatic and asymptomatic) occurring during the study should 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.
For each of the timepoints (Weeks 52 and 78), a binary variable will be derived, on a subject-by-subject basis, as follow:

- No (0): no new episodes and no worsening from baseline of vertebral fragility fracture until Week XX
- Yes (1): presence of new episodes or worsening from baseline of vertebral fragility fracture until Week XX

where, Week XX is the time point of interest.
In order to mitigate the risk associated with non-evaluable X-ray on certain vertebras (i.e., the assessment is received as “NOT ASSESSABLE” for a vertebra from the external vendor), as an additional sensitivity analysis, the worst case scenario is considered and such NOT ASSESSABLE results will be considered as new fractures on the relevant vertebra.
Of note: two datasets are received from external vendor for x-ray reading, these are MO and SMO; as per vendor instructions SMO corresponds to secondary read data that are not to be included in the statistical analysis; therefore, for any derivation based on x-ray reading described in this SAP, the dataset MO will be the only one considered; data results received in SMO will be displayed in the data listings with a clear identification key for results coming from MO versus SMO.

4.3.1.1.5 Non-vertebral fragility fracture incidence

Information on any non-vertebral fractures while in the study will be recorded as AEs, collected AEs will be scrutinised by Medical Monitor to flag non-vertebral fracture events. The diagnosis

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

For each of the timepoints (Weeks 52 and 78), a binary variable will be derived as follow:

- No (0): no AE episodes of non-vertebral fragility fracture until Week XX
- Yes (1): AE episodes of non-vertebral fragility fracture until Week XX

where, Week XX is the time point of interest.

4.3.1.2 Secondary Efficacy – Main Analytical Approach

Secondary efficacy analyses will be executed based on the on FAS and PPS.

MI will be conducted for %CfB in lumbar spine BMD at Week 78, as per below section 4.3.1.2.2.

No imputation of missing data is foreseen for other secondary endpoints.

4.3.1.2.1 %CfB in total hip BMD at Weeks 26, 52 and 78

BMD, CfB and %CfB of secondary BMD endpoints, %CfB will be estimated for each treatment arm and 95% CI derived for each time point. BMD, CfB and %CfB will be summarised in FAS and PPS.

Furthermore, the endpoints %CfB in total hip BMD at Weeks 26 and 52 will be analysed by using mixed model for repeated measures (MMRM) with the following factors:

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

Unstructured covariance matrix will be used. In case of convergence issues, alternative structures will be considered in the following order: Autoregressive(1), Compound Symmetry, Toeplitz; until convergence is met. MMRM will be executed without MI applied, without special handling of ICEs.

By-subject listing will be provided.

4.3.1.2.2 %CfB in lumbar spine BMD at Weeks 26, 52 and 78

Similar analysis as detailed in section 4.3.1.2.1.

In addition, for FDA, a sensitivity tipping point analysis will be conducted to assess the robustness of the results at Week 78: a similar analysis will be performed as the one described on this SAP at section 4.2.1.3.2 will be performed by using Week 78 BMD data. As the transition period consists of three study arms, the arm 'Prolia to Prolia' will be considered as the reference arm and the two arms 'RGB-14-P to RGB-14-P' and 'Prolia to RGB-14-P' will be test arms and will be compared to the 'Prolia to Prolia' reference. Again, assessments of the primary endpoints observed after occurrence of ICE2 will be disregarded, i.e., artificially set as missing, and will be imputed in the tipping point analysis with same MI techniques as applied to regular missing data. Different assumptions will be made for missing values (and post-ICE2 assessments) in each of the three arms. SAS PROC MI will be utilised with MNAR statement including ADJUST option with SHIFT as sub option to allow the Week 78 outcomes in the three treatment arms to vary independently.

For the method implementation, similar steps will be followed as described in section 4.2.1.3.2, including both approach 1 and approach 2; Week 52 lumbar spine BMD %CfB will be included in the FCS REG statement of the PROC MI in the Steps 3 and 4 predictive variable for the missing (originally or post-ICE2 assessments) Week 78 outcomes.

Results obtained while running the approach 1 and approach 2 will be tabulated, including the shift applied to reference arm 'Prolia to Prolia' and to the test arms, the point estimate obtained for the primary endpoint together with the two-sided 90% CIs and the standard error. For different combinations of reference and test arms shifts:

- observed LCL will be plotted when testing non-inferiority, UCL when testing non-superiority
- forest plots will also be present, plotting point estimate and 90% CIs under the non-inferiority and non-superiority tests

4.3.1.2.3 %CfB in femoral neck BMD at Weeks 26, 52 and 78

Similar analysis as detailed in section 4.3.1.2.1.

4.3.1.2.4 Vertebral fragility fracture incidence

All data on Vertebral fractures will be listed. A summary table will also be presented with number of subjects who experienced at least one fracture in the study (starting from randomisation) and total amount of post-randomisation fractures.
Incidence of fracture will be estimated as the proportion (also presented as percentage) of subjects with at least one post-randomisation fracture, and a two-sided 95% CI will be computed. Average difference and its 95% CI will be also computed.

4.3.1.2.5 Non-vertebral fragility fracture incidence

Similar analysis as detailed in section 4.3.1.2.4.

4.3.1.3 Secondary Efficacy – Sensitivity Analyses

Not Applicable.

4.3.1.4 Secondary Efficacy – Supplementary Analyses

Not Applicable.

4.3.2 Secondary Pharmacodynamic Endpoints

4.3.2.1 Secondary Pharmacodynamic – Definition of Endpoint(s)

Of note: pharmacodynamic results are received from external vendor laboratory; in some instances, P1NP results are received with the two test codes ZP1NG and ZP1NB; in these

instances, based on instructions received from laboratory, the results received under code ZP1NG is to be considered as latest and more accurate and used for summaries, analysis and any derivation detailed in this SAP; both results obtained under ZP1NG and ZP1NB will be displayed in the data listings, with a clear identification key for results received under code ZP1NG and under code ZP1NB.

4.3.2.1.1 %CfB in serum P1NP at Weeks 4, 26, 52 and 78.

For %CfB derivation of this secondary pharmacodynamic endpoint, same formula will be used as for sCTX %CfB, please refer to section 4.2.2.1.

4.3.2.1.2 %CfB in sCTX at Weeks 4, 26, 52 and 78.

For sCTX %CfB derivation, please refer to section 4.2.2.1.

4.3.2.2 Secondary Pharmacodynamic – Main Analytical Approach

Secondary pharmacodynamic analyses will be executed on PDS.

4.3.2.2.1 %CfB in serum P1NP at Weeks 4, 26, 52 and 78.

Descriptive analysis of P1NP, CfB and %CfB at each visit will be presented. Furthermore, a by-subject listing will be provided. P1NP concentrations below the limit of quantification (BLQ) will be presented as BLQ in listing. In summary tables, values BLQ will be imputed as LLOQ.

4.3.2.2.2 %CfB in sCTX at Weeks 4, 26, 52 and 78.

Descriptive analysis of sCTX, CfB and %CfB at each visit will be presented. Furthermore, a by-subject listing will be provided.

4.4 Immunogenicity Analysis and Serum drug concentrations

4.4.1 Immunogenicity

Immunogenicity analyses will be executed on IAS, unless otherwise specified.

4.4.1.1 Immunogenicity binding ADAs and NAbs – Definition of Endpoint(s)

Antibodies to denosumab (ADA) and neutralising antibodies (Nabs) will be evaluated in serum samples collected at Weeks 0, 2, 4, 26, 28, 30, 52, 54, 56 and 78.

Serum immunogenicity samples will be assessed for ADAs and NAbs according to the following stepwise analytical approach, visit wise:

1. Screening analysis (assay): all immunogenicity samples are analysed in an ADA screening assay, this will give a result of positive/negative, which tells if the samples are potentially positive for ADA or not
2. For those who had a positive screening result, confirmatory analysis is performed: confirmatory assay giving a result of positive/negative, which tells with certainty that the sample is positive for ADA or not
3. Confirmed ADA positive samples will be titrated
4. Confirmed ADA positive samples will be analysed in NAb assay, which may result to be either positive or negative

4.4.1.2 Immunogenicity – Main Analytical Approach

All immunogenicity results (ADA Screening positive or negative, ADA positive or negative, ADA titres, NAb positive or negative) will be listed by subjects and treatment group, at each visit where they are assessed for main and transition period for full analysis set.
Incidence of binding ADAs and Nabs in samples by visit and titre ranges will be summarised for the main (0-w52) and transition period (0-w78) for each time points, based on IAS.

ADA status of subjects

Overall, subjects will be labelled as ADA negative or positive as per the logic outlined in Table 6.

Table 6 – Overall ADA status classification

Subject overall classification	Baseline* result	Post-dose visit results

		(up to week 52 for the main period; up to week 78 for the transition period)
Negative	Negative	Negative
Negative	Positive	Negative/ Positive (no significant ADA titer increase from baseline at any post-baseline timepoint)
Positive	Negative	Positive (any titre level, observed at least at one post-baseline timepoint)
Positive	Positive	Positive (significant ADA titer increase from baseline, observed at least at one post-baseline timepoint)
Switch-induced and boosted positives, if any, will be evaluated based on the individual immunogenicity response kinetics by Sponsor in the CSR. *Baseline is the last result obtained before the first injection		

In those subjects with baseline ADA positivity, a significant ADA titer increase from baseline is defined as minimum 4-fold increase in titre ratio, corresponding to a 75% increase.
Titer ratio = Post-dose titer / Baseline titer (last assessment available pre first dosing)
Titer ratio ≥ 4 will be interpreted as significant ADA titer increase from baseline.

If necessary, data will be reviewed by the immunogenicity laboratories personnel who will discuss on a case-by-case basis the special features and exceptions to the logics above described; if these decisions will be evaluated prior than unblinding, these will be communicated in a blinded way to the main study team, handling strategies defined in the final BDRM / DRM report as applicable.

NAb status

Subjects are not expected to be NAb positive at pre-treatment, exceptional cases of subjects NAb positive at baseline and other data issues will be reviewed by the immunogenicity laboratories personnel who will discuss on a case-by-case basis the special features and exceptions to the logics above described; if these decisions will be evaluated prior than unblinding, these will be communicated in a blinded way to the main study team, handling strategies defined in the final BDRM / DRM report as applicable.

Overall, subjects will be labelled as NAb negative or positive as per the below logic outlined in Table 7.

Table 7 – Overall NAb status classification

Subject overall classification	Baseline* result	Post-dose visit results (up to week 52 for the main period; up to week 78 for the transition period)
Negative	Negative/ not tested	Negative
Positive	Negative/ not tested	Positive
Unexpected, if will be observed, will be discussed at the BDRM	Positive	Negative / Positive

*Baseline is the last result obtained before the first injection

Nab status of subjects will be summarised for the main period by treatment arms and overall.

4.4.1.3 Immunogenicity – Supplementary Analysis

Persistent versus transient ADA response

For overall ADA positive subjects, determination of Persistent versus transient ADA response will be studied based on indications from Shankar (2014) [17].

Persistent ADA response is defined as:

1) ADA positivity detected at two or more sampling time points where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks (112 days) or longer

   or

2) ADA positivity detected in the last available sampling time point

   or

3) Last ADA positivity detected is not followed by a negative sample dated 16 weeks (112 days) or longer after such positivity.

In other words, persistent ADA response is defined:

- when a subject has at least two post baseline positive results and (date of last post baseline positive result – date of first post baseline positive result) + 1 is ≥ 112 days, then the subject will be flagged as with persistent ADA response
- when the last available assessment for the subject indicates positive ADA, then the subject will be flagged as with persistent ADA response
- if the last post baseline positive result for a subject is not followed by a negative result distanced 112 days or more from such positive result, then the subject will be flagged as with persistent ADA response
- in any other case, then the subject will be flagged as with transient ADA response

In main period summary, all the data up to the pre-dose week 52 assessment will be used.
Example cases are provided in appendix 6.4.10, Table 13.

Transition period ADA and Nab shift of status

For subjects included in the transition period, a shift table will be produced which will show shifts in the overall ADA and Nab positive / negative status when switching from main to transition treatment. For ADA, the persistent and transient responses .

4.4.2 Serum drug concentrations – Supporting immunogenicity

Serum drug concentrations will be listed, as received from vendor, by subjects and treatment group, at each visit where they are assessed for main and transition period. Denosumab concentration data may be used for interpretation of immunogenicity, safety, efficacy aspects of study, but will not be evaluated statistically. Parexel will not perform any statistical analysis nor summaries for serum drug concentrations nor parameters.

4.5 Safety Analyses

Safety variables are:

- Exposure
- Adverse event (AE) assessments
- 12-lead electrocardiograms (ECG): PR interval, QRS interval, QT interval, QTC interval and correction type
- Vital signs: body temperature, blood pressure, heart rate, respiratory rate
- Physical examinations
- Clinical laboratory tests (haematology, clinical chemistry, and urinalysis parameters)
- Concomitant medication assessments
- Number and intensity of injection site reaction

In general, if not stated otherwise, the safety variables will be listed in the SAF for the main period. This will allow to have listings on all treated subjects. When producing main period TFLs, only data included in the main period milestone data freezing scope will be printed in listing, while when producing TFLs for the whole study, all the data will be printed in listings

including data pertinent to the transition period. Detailed strategy for main and transition period deliverable is in section 1 of this SAP.

4.5.1 Extent of Exposure

IMP dosing information will be listed by subject and includes:

- Anatomical Location (upper arm, abdomen, thigh)
- Laterality (left, right, other/specification)
- Route (subcutaneous)
- Administration date
- Administration start time (24h HH:MM)
- Kit number

Summaries will be provided based on FAS for number of subjects treated and not treated with each scheduled injection.

4.5.2 Adverse Events

An AE is any untoward medical occurrence in a study subject administered an IMP which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Adverse events may include the onset of new illness and the exacerbation of pre-existing conditions.
Other untoward events occurring in the framework of a clinical study will be recorded as AEs, e.g., those occurring during treatment-free periods (including Screening or post-treatment Follow-up periods), in association with study-related procedures and assessments.
Concomitant illnesses, which existed before entry into the clinical study, will not be considered AEs unless they worsen during the study. Pre-existing conditions will be recorded as part of the subject's medical history.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher. Safety population data sets (SAF) will be used for safety analysis.
A treatment emergent adverse event (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.
In the Main and Transition Period, TEAEs will be additionally assigned to the treatment to which the AE was emergent. When time of onset is available, time of onset will be used for the derivation of the treatment emergent flag. AE emerging on an injection day will be assumed to be emergent to such injection treatment period, unless there is clear evidence through times comparison that the event started prior than the injection.
AEs with incomplete start and end dates are not expected. In case of any AEs with incomplete start and end dates, below rules will apply:

- Adverse events with completely unknown start date will be considered as TEAEs
- Adverse event with unknown start day and month but with known start year will be considered:
    - as TEAEs if the start year coincides or is after the dosing year
    - as non TEAEs if start year is before the dosing year
- Adverse events with unknown start day but with known start month and year will be considered:
    - as TEAEs if the start month and year coincide or are after the dosing month and year
    - as non TEAEs if start month and year are before the month and year of first dosing
- Adverse events with completely unknown end date will be considered as ongoing (not recovered/ not resolved) on the day of last contact with the subject.

For any AEs, severity was scored in a five-point scale as mild, moderate, severe, life threatening and death. To be noted that both the wording “severity” and “intensity” were interchangeably used in the CSP and eCRF, with the same meaning.

Local tolerance will be evaluated through skin examination, events of intolerance will be regarded as ISR. The grading of ISRs will be based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5. Injection site reactions with a grading of ≥ 1 are expected to be recorded as AEs in the eCRF AE log form. Local tolerance listing will be provided, while ISRs will be listed and also included in the TEAEs summaries.

Separate summaries will be produced for the AEs and TEAEs emerging in main and transition period regarding the below outputs:

- An overview on the number and percentage of subjects (and number of events) with:
  - Any AE (only applicable for the main period summaries)
  - Any TEAE
  - Any TEAE severe or with worse severity
  - Any treatment related TEAE
  - Any treatment related TEAE severe or with worse severity
  - Any serious TEAE
  - Any serious TEAE severe or with worse severity
  - Any treatment related serious TEAE
  - Any treatment related serious TEAE severe or with worse severity
  - Any non-serious TEAE
  - Any AE leading to subject discontinuation (only applicable for the main period summaries)
  - Any TEAE leading to subject discontinuation
  - Any treatment related TEAE leading to subject discontinuation
  - Any fracture TEAE
  - Any fracture TEAE severe or with worse severity
  - Any treatment related fracture TEAE
  - Any treatment related fracture TEAE severe or with worse severity
  - Any serious fracture TEAEs

- Any serious fracture TEAEs severe or with worse severity
- Any treatment related serious fracture TEAE
- Any treatment related serious fracture TEAE severe or with worse severity
- Deaths
- Any AE leading to death (only applicable for the main period summaries)
- Any TEAEs leading to death
- Any treatment related fatal serious TEAEs
- Any injection site reactions
- Any injection site reactions severe or with worse severity
- Any injection site reactions of CTCAE grade ≥ 3

- Number and percentage of subjects for each TEAE, and non-serious TEAE categorised by treatment, SOC and PT
- Number and percentage of subjects for each TEAE severe or with worse severity, categorised by treatment, SOC and PT
- Number and percentage of subjects for each TEAE categorised by treatment, SOC, PT, and worst severity
- Number and percentage of subjects for each treatment related TEAE categorised by treatment, SOC and PT
- Number and percentage of subjects for each treatment related TEAE severe or with worse severity categorised by treatment, SOC and PT
- TEAEs in ≥ 3% of subjects by treatment, SOC and PT
- Treatment related TEAEs in ≥ 3% of subject by treatment, SOC and PT
- TEAEs in ≥ 5% of subject by treatment, SOC and PT
- Treatment related TEAEs in ≥ 5% of subject by treatment, SOC and PT
- Non-serious AEs in ≥ 3% of subject by treatment, SOC and PT
- Non-serious AEs in ≥ 5% of subject by treatment, SOC and PT

A detailed list of all AEs, including TEAEs, adverse reactions (i.e., AEs related with the IMP), SAEs, ISR and fractures will be created.

AEs listing will be presented by treatment group and will include as a minimum: subject identifier, age, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, severity, seriousness, action taken, outcome and causality.

Adverse event summaries will be ordered by descending order of total frequency (across all study parts treatment groups combined) for SOC, and PT within SOC. In the event of PTs with equal total frequencies, the relevant PTs will be sorted alphabetically.

Note for subjects enrolled in the transition period: TEAEs emerging prior to third injection will be summarised in main tables only, even though lasting during the transition period as well, these events will not be counted in the transition tables; TEAEs emerging on or after the third injection will be summarised in transition tables only.

If an AE starts in the main period and worsens in severity during the transition period, study sites will communicate in eCRF the end date for the AE with the first severity and will register in eCRF a new AE with the worse severity for transition period.

If a subject reports the same TEAE more than once within that SOC and PT, the TEAE with the highest severity will be used in the corresponding severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries. If severity or causality is missing, a conservative approach for AE assessment (taking into account the worst case) will be followed.

If a device incident or device deficiency cause an AE or SAE during the study, the unblinded study team member will complete the Product Complaint Form. Upon the relevant study period unblinding, such forms will be shared to the statistical team for processing. Listing for any device incident or device deficiency will be created.

4.5.2.1 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Summaries detailed below will be provided for deaths, SAEs and other significant AEs presented by treatment group:

- Number and percentage of subjects for each treatment emergent SAE, categorised by SOC and PT

- Number and percentage of subjects for each treatment emergent SAE severe or with worse severity, categorised by SOC and PT
- Number and percentage of subjects for each treatment emergent SAE, categorised by SOC, PT, and worst severity
- Number and percentage of subjects for each treatment related SAE, categorised by SOC and PT
- Number and percentage of subjects for each treatment related SAE severe or with worse severity, categorised by SOC and PT
- Number and percentage of subjects for each TEAE leading to subject discontinuation, categorised by SOC and PT
- Number and percentage of subjects for each related TEAE leading to subject discontinuation, categorised by SOC and PT
- Number and percentage of subjects for each treatment emergent fracture AE, categorised by SOC and PT
- Number and percentage of subjects for each treatment emergent fracture AE severe or with worse severity, categorised by SOC and PT
- Number and percentage of subjects for each treatment emergent fracture AE, categorised by SOC, PT, and worst severity
- Number and percentage of subjects for each treatment related fracture AE, categorised by SOC and PT
- Number and percentage of subjects for each treatment related fracture AE severe or with worse severity, categorised by SOC and PT
- Number and percentage of subjects for each treatment emergent serious fracture AE, categorised by SOC and PT
- Number and percentage of subjects for each treatment emergent serious fracture AE severe or with worse severity, categorised by SOC and PT
- Number and percentage of subjects for each treatment emergent serious fracture AE, categorised by SOC, PT, and worst severity

- Number and percentage of subjects for each treatment related serious fracture AE, categorised by SOC and PT
- Number and percentage of subjects for each treatment related serious fracture AE severe or with worse severity, categorised by SOC and PT
- Number and percentage of subjects for each fatal SAE, categorised by SOC and PT
- Number and percentage of subjects for each treatment related fatal SAE, categorised by SOC and PT
- Number and percentage of subjects for each injection site reaction, categorised by SOC and PT
- Number and percentage of subjects for each injection site reaction severe or with worse severity, categorised by SOC and PT
- Injection Site Reactions of CTCAE grade ≥ 3 by Treatment, System Organ Class and Preferred Term

For deaths, SAEs and other significant AEs the following listing will be provided:

- A by-subject listing of all deaths that occurred during the study, including details such as cause of death from eCRF page Death
- A by-subject listing of adverse events leading to death
- A by-subject listing of related adverse events leading to death
- A by-subject listing of all serious adverse events
- A by-subject listing of all related serious adverse events
- A by-subject listing of all fracture adverse events
- A by-subject listing of all related fracture adverse events
- A by-subject listing of adverse events leading to discontinuation
- A by-subject listing of related adverse events leading to discontinuation
- A by-subject listing of all adverse events severe or with worse severity
- A by-subject listing of all related adverse events of severe or with worse severity
- A by-subject listing of all injection site reactions.

4.5.3 Additional Safety Assessments

4.5.3.1 Clinical Laboratory Evaluation

The tests detailed in Table 8 will be performed by the central laboratory. All study-required laboratory assessments will be performed by a central laboratory, except for:

- Dipstick urinalysis at all visits
- Immunogenicity and serum drug concentration samples (assessed by Sponsor)

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.

For clinical study report purposes, the values from the central laboratory will be considered. Local laboratory results are required in the event that the central laboratory results are not available in time for IMP administration as indicated in the SoA (section 6.2.10 and Table 11) and/or for response evaluation. 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.

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

Investigators will receive central laboratory safety report in paper, and they must document their review of each laboratory within the paper safety report itself, including assessment of clinical significance. No clinical significant assessment will be registered in central laboratory eCRF page, however clinically significant abnormal values will be logged as AEs into the AE eCRF page. Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Table 8 - Protocol-Required Safety 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 Magnesium Phosphorus	AST ALT Alkaline phosphatase GGT Total and direct bilirubin Total Protein Albumin Total cholesterol Triglyceride LDH 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

Laboratory Assessments	Parameters

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

By-subject listing will be provided for all subjects enrolled by visit, including changes from baseline and reference range. Laboratory values will be summarised for all visits scheduled in Main and Transition period. Unscheduled visits will be listed only, unless contribute to baseline measurement or replace a missing visit assessment as detailed in section 4.1.6 of this SAP. Abnormal (for haematology, clinical chemistry or urinalysis) results will be also provided as by-subject listing.

All values outside the clinical reference ranges will be flagged in the data listing. The abnormal values will be flagged with 'Low' for values below the lower limit of the clinical reference range and 'High' for values above the upper limit of the clinical reference range and included in the listing. Moreover, lab results will be compared with corresponding normal ranges and following categories will be derived and presented in listing:

- NR [within Normal Range]
- OoR ≤ 2x NR [Out of Range ≤ 2x NR in both directions]
- OoR ≤ 5x NR [OoR >2x to ≤ 5x NR in both directions]
- OoR > 5x NR [OoR > 5x NR in both directions]

The following summaries will be provided for all parameters:

- A summary of results by treatment arm and visit
- A summary of the change from baseline by treatment arm and visit.
- Shift tables by treatment group and visit will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the visit's observed value; in shift tables the denominator for the percentages will be based on observations non-missing for baseline and the pertinent visit.

- hematology and clinical chemistry shift table to evaluate whether a particular laboratory test value was normal, low or high for each visit value relative to the baseline value presented as well as normal, low or high
- hematology and clinical chemistry shift table to evaluate whether a particular laboratory test value was within NR, OoR ≤ 2x NR, OoR ≤ 5x NR or OoR > 5x NR for each visit value relative to the baseline value presented as well as NR, OoR ≤ 2x NR, OoR ≤ 5x NR or OoR > 5x NR
- urinalysis shift table to evaluate whether a particular laboratory test value was normal, or abnormal for each visit value relative to the baseline value presented as well as normal or abnormal

4.5.3.2 Vital Signs, Physical Findings and Other Observations Related to Safety

4.5.3.2.1 Vital Signs

Vital signs will be assessed as shown in the SoA (Table 10 and Table 11). The following vital signs measurements will be obtained:

- Body temperature (C° or F°) and temperature measurement location (axilla, tympanic membrane and forehead)
- Respiratory Rate (breaths/min)
- Heart Rate (beats/min)
- Blood pressure and subject position during assessment (sitting, standing and supine)
  - Systolic blood pressure (SBP) (mmHg)
  - Diastolic blood pressure (DBP) (mmHg)

Temperature values recorded as °F will be summarised as °C using the function below:

$$°C = (°F - 32) \times \frac{5}{9}$$

For body temperature measurements in degrees of Fahrenheit, both °F and °C values and units will be reported in line listing. Body temperature values obtained from different body parts will

be summarised separately by measurement location in the order of axilla, tympanic membrane, and forehead.

Vital signs data will be listed by subject including changes from baseline. Descriptive statistics for absolute values and changes from baseline will be presented by Treatment Period, Treatment Arm, visit and overall.

4.5.3.2.2 ECG

Standard safety 12-lead ECGs will be performed as shown in the SoA (Table 10 and Table 11).

The following ECG parameters will be recorded:

- PR-interval (msec).
- QRS-complex (msec).
- QT-interval (msec).
- QTcF (msec) or QTcB (msec) or QTc 'other' (msec).

The ECG will be evaluated by the Investigator as normal/abnormal and clinically/not clinically significant.

All ECG parameters will be listed by subject including changes from baseline. Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline will be presented by study part, treatment group and overall.

Three QTc types may be collected: QTcF, QTcB and Other QTc; these will be summarized as three parameters, with CfB being calculated only when the post-baseline QTc type matches the baseline one.

4.5.3.2.3 Physical Examination

Physical examinations will be performed as shown in the SoA (Table 10 and Table 11).

The physical examination includes an assessment of general appearance and a review of systems (head, eyes, ears, nose, mouth - oral cavity – throat – neck, thyroid gland, lymphatic gland, dermatologic, respiratory system, cardiovascular system, gastrointestinal, extremities, musculoskeletal and neurological system).

For each time point, an overall interpretation will be recorded by the Investigator as normal, abnormal not clinically significant, or abnormal clinically significant.
A summary of the number and percentage of subjects in each category (normal, abnormal NCS and abnormal CS) will be provided by Treatment Period, Treatment Arm, visit and overall.
By-subject listing will be provided for all subjects.

4.5.3.2.4 Overdose

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.

4.5.3.2.5 Pregnancy test

A Pregnancy test will be executed as shown in the SoA (Table 10 and Table 11) in subjects, even though pregnancy is not expected (postmenopausal population). By-subject listing will be provided for all subjects.

4.6 Other Analyses

4.6.1 Other Variables and/or Parameters

4.6.1.1 Health Economics

Not applicable.

4.6.1.2 Patient Reported Outcome (PRO) Measures

Not applicable.

4.6.2 Subgroup Analyses

No subgroup analyses are planned.

For the summaries and analyses, the term ‘Centre’ will be used to define each investigator site. Otherwise specified, analyses will not be presented by centre or geographical region.

4.6.3 Pharmacokinetics, Pharmacokinetic-Pharmacodynamic Relationships

Serum drug concentrations at immunogenicity measurement time points will be listed as supporting data for immunogenicity evaluation (possible drug interference).

4.7 Interim Analysis

No interim analysis will take place.

4.8 Changes to Protocol-planned Analyses

Analyses described in this SAP are in alignment with the study protocol.

5 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 [13], [14], [15], sample size was calculated from the following parameters:

- The primary parameter is the %CfB in lumbar spine BMD
- Two-sided 95% CIs of the difference between the study arms must be contained within the 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)
- The expected (true) common standard deviation is 3.44

Based on the above assumptions the total evaluable sample size required for efficacy comparison with a margin of CCI [redacted] power of 90% is 362 (181 per arm)
With regards to the PD co-primary endpoint, healthy volunteer data [15] was used for the sample size calculations due to the lack of information on AUEC sCTX0-m6 derived from the subject 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 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 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) provides the probability for a sample size (N) of 60 and 66 participants to observe at least 1 participant per AE, considering different frequencies of AE.

Table 9 - 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.

6 Supporting Documentation

6.1 Appendix 1: List of Abbreviations

List and define all acronyms and abbreviations used in the document here. Abbreviations should be spelled out in full, and the abbreviation indicated in parentheses at first appearance in the text. Abbreviations should appear in alphabetical order.

Abbreviation / Acronym	Definition / Expansion
%CfB	Percentage of Change from Baseline
δ_{PST}	$\delta_{\text{principal stratum}}$
ADA	Anti-Drug Antibodies
AE	Adverse event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUEC	Area Under the Effective Curve
BDRM	Blinded Data Review Meeting
BDRR	Blinded Data Review Report
BMD	Bone Mineral Density
BMI	Body Mass Index
BP	Blood Pressure
Bpm	Beats per minute
BUN	Blood Urea Nitrogen
CfB	Change from Baseline
CI	Confidence interval
CRF	Case Report Form
CRP	C-Reactive Protein

Abbreviation / Acronym	Definition / Expansion
CS	Clinically Significant
CSP	Clinical Study Protocol
CTCAE	Common Terminology Criteria for Adverse Events
DB Lock	Database Lock
DBP	Diastolic Blood Pressure
DXA	Dual Energy X-Ray Absorptiometry
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ENR	Enrolled Analysis Set
EOS	End-of-study
EST	Erythrocyte Sedimentation Rate
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GDO	Global Data Operations
GGT	Gamma-Glutamyl Transferase
GLMM	Generalised Linear Mixed Models
HbcAg	Hepatis B core antigen
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	Heart rate
IAS	Immunogenicity Analysis Set

Abbreviation / Acronym	Definition / Expansion
ICE	Intercurrent Events
ICF	Informed Consent Form
IgC	Immunoglobulin
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IRIS	Inconclusive Results or Insufficient Sample volume
IQC	Calibration of DXA scanners using phantom data
ITT	Intent To Treat
LCL	Lower Confidence Limit
LDH	Lactate Dehydrogenase
MAR	Missing at random
MCAR	Missing completely at random
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
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
NA	Not available
NAb	Neutralising Antibodies
NCS	Not clinically significant
NK	Not known
NR	Normal Range
P1NP	Prokollagen Typ 1 N-terminales Propeptid

Abbreviation / Acronym	Definition / Expansion
PD	Pharmacodynamic
PDS	Pharmacodynamic analysis set
PK	Pharmacokinetic
PP	Per-Protocol
PPS	Per-Protocol Analysis Set
PPSC	Per-Protocol and Completer
PSE	Principal Stratum Estimand
PST	Principal Stratum
PT	Preferred Term
PTH	Parathyroid Hormone
QT	The QT interval is measured from the beginning of the QRS complex to the end of the T wave
QTc	Corrected QT interval
QTcB	QT corrected using Bazett's formula
QTcF	QT corrected using Fridericia's formula
RBC	Red Blood Cell Count
SACE	Survivor Average Causal Effect
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SBP	Systolic blood pressure
sCTX	Serum type I collagen C-telopeptide
SD	Standard deviation or single dose
SE	Standard error of the mean
SoA	Schedule of Assessments

Abbreviation / Acronym	Definition / Expansion
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
SUTVA	Stable Unit Treatment Values Assumption
TEAE	Treatment-emergent adverse event
TPE	Treatment Policy Estimand
TSH	Thyroid-Stimulating Hormone
TTATP	Time to ADA Treatment induced or boosted Positivity
UCL	Upper Confidence Limit
US	United States
WBC	White Blood Cell Count
XCAL	DXA Inter-scanner cross-calibration

6.2 Appendix 2: Supporting Study Information

In general, if not stated otherwise, the variables in this section will be listed in the FAS for the main period. This will allow to have listings on all randomized subjects. When producing main period TFLs, only data included in the main period milestone data freezing scope will be printed in listing, while when producing TFLs for the whole study, all the data will be printed in listings including data pertinent to the transition period. Detailed strategy for main and transition period deliverable is in section 1 of this SAP.

6.2.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided in the ENR, from screening to study completion.

By-subject listing will include:

- ICF date and response by subject
- Visit Dates
- Randomisation listing, including: 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.
- Subject's discontinuation, including the date of study exit, duration of treatment (i.e., number of IMP doses received) and reason for discontinuation.
- Subjects excluded from each analysis sets, including the reason for exclusion.

Summaries will include number and percentage of:

- Screened subjects
- Randomised subjects
- Treated subjects
- Subjects completed the study
- Subjects withdrawn and reason for end of treatment and end of study

6.2.2 Demographics

Descriptive statistics (see section 4.1.1) for demographics and anthropometric variables will be listed and summarised in the FAS.
Demographic variables include:

- Age (years)
- Sex (Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other/Specification)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)

Anthropometric variables include:

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

Weight will be listed both as originally collected and in kg. Weight values collected as lb will be converted in kg (kg = 2.20462 * lb) for analyses. Height will be listed both as originally collected and in cm. Height values collected as in will be converted in cm (cm = 2.54 * in) for analyses.

6.2.3 Baseline and Disease Characteristics

In the study, sites will enter the osteoporosis diagnosis in the medical history page for subjects with a known prior diagnosis of osteoporosis. For those subjects who received osteoporosis diagnosis during the study screening period, the diagnosis will not be recorded neither as a medical history nor as an AE event. Subjects will then be flagged as:

- ‘Subjects with prior osteoporosis diagnosis’ if the osteoporosis diagnosis is in the medical history page
- ‘Subjects with new osteoporosis diagnosis’ if the osteoporosis diagnosis is not in the medical history page

Above flag will be reviewed and confirmed by medical monitor. Summaries will be provided to provide number of subjects with prior or new diagnosis.
Serology will be tested at screening, including HBV, HCV and HIV. In the FAS, results will be listed; summary table will be presented for number of subjects reactive to each tested virus.

6.2.4 Treatment Compliance

Not applicable.

6.2.5 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol.
In the FAS, a summary of the number and percentage of subjects with a major protocol deviation by study period, and treatment will be provided for each country/site and overall. By-subject listing of all protocol deviations will be provided.
The COVID-19 pandemic requires specific attention on the protocol deviations that may impact the conduct of the study and the follow-up of the subjects. The number and percentage of subjects who experienced at least one COVID-19 deviation will be described together with the major protocol deviation table. Also, protocol deviations that are specifically related to COVID-19 will also be described in a separate table and identified in the listing of deviations.

Blinded assessment at the end of Main Treatment Period

Deviations will be reviewed and classified in a blinded fashion at the Blinded Data Review Meeting (BDRM) prior to unblinding at the end of Main Treatment Period. The BDRM will be performed to confirm that the database is ready to be hard locked for the Treatment Periods 1 and 2, all protocol deviations addressed with the assigned classification (i.e., Minor/Major) together with their overall effect on a subject, and to agree assignment of each subject to the analysis populations. During BDRM, all protocol deviations and their possible impacts will be discussed between Parexel and the Sponsor and will be assessed as “minor” or “major”.
Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments.

Major protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

Major protocol deviations and protocol deviations affecting efficacy and/or safety can lead to the exclusion of a subjects from the PPS. Reasons for excluding subjects from any study populations will be reported and described in the BDRM Report that will be finalised before unblinding procedures for study reporting. Listing of assignment of each subject to each analysis set will be provided.

Blinded assessment at the end of Transition Period

Deviations from the Transition Period will as well be reviewed and classified in a blinded fashion in a BDRM prior to final Data Base Lock. The BDRM will be performed to confirm that the database is ready to be fully hard locked, all protocol deviations addressed with the assigned classification (i.e., Minor/Major) together with their overall effect on a subject. It is expected that PDs collected during the Transition Period will not modify assignment of each subject to the analysis populations as these were decided at the BDRM for the main study part.

6.2.6 Medical and Surgical History and Concurrent Illnesses

In the FAS, medical and surgical history data will be listed by subject including visit, description of the disease/procedure, MedDRA system organ class (SOC) and preferred term (PT) (MedDRA version 24.0 or higher), start date and stop date (or ongoing if applicable).

6.2.7 Prior/Concomitant Medications

In the Main and Transition Period, prior medications are those that started and stopped prior to the first dose of IMP. Concomitant medications are those taken after first dosing (including medications that started prior to dosing and continued after). In the Main and Transition Period, a concomitant flag will be additionally created to identify the treatment to which the medication was concomitant:

- Concomitant medication in the main period is defined as any medication ongoing at the first dose of IMP or with a start date on or after the first dose of IMP and before the third injection
- Concomitant medication in the transition period is defined as any medication ongoing at third injection or with a start date on or after the third injection

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first IMP dosing. Medications will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication stopped prior to the first IMP dosing. If there is clear evidence to suggest that the medication stopped prior to the first IMP dosing, the medication will be assumed to be Prior.
Prior and concomitant medications will be coded according to the World Health Organisation Drug Dictionary latest version.
In the FAS, prior and concomitant medications will be listed by subject and will include the following information: reported term, trade name, the route of administration, dose, frequency, start date/time, stop date/time and indication. Prior and concomitant medications will also be summarised by ATC level 4 term and trade name, for the main and transition period.

6.2.8 Prohibited therapies

Unless required for AE/SAE management, the medications and interventions which are listed below are prohibited during the study period:

- Any osteoporosis treatment (other than calcium and vitamin D supplements).
- Products containing denosumab (e.g., Xgeva®) or biosimilar denosumab.
- Romosozumab.
- Cathepsin K inhibitors.
- Strontium or fluoride (except topical use in toothpaste).
- Intravenous or oral bisphosphonates.
- Teriparatide, abaloparatide or any PTH analogues.

- Tibolone, oral or topical (e.g., transdermal, intravaginal) oestrogen, antioestrogens, SERMs and aromatase-inhibitors.
- Calcitonin or its derivates and calcimimetics (such as cinacalcet or 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.

As far as possible, prohibited therapies will be flagged programmatically based on ATC and MedDRA codes, as applicable, however final list of the prohibited therapies will be reviewed and confirmed by the medical monitor at the BDRM, at which time subjects who assumed prohibited therapies will be clearly flagged.
In the FAS, prohibited therapies will be listed by subject.

6.2.9 Concomitant Procedures

In the Main and Transition Period, procedures that started and stopped prior to the first dose of IMP will be considered as prior procedures. Concomitant procedures are those happening after first dosing (including procedures that started prior to dosing and continued after). In the Main and Transition Period, a concomitant flag will be additionally created to identify the treatment to which the procedure was concomitant:

- Concomitant procedure in the main period is defined as any procedures ongoing at the first dose of IMP or with a start date on or after the first dose of IMP and before the third injection

- Concomitant procedure in the transition period is defined as any procedures ongoing at third injection or with a start date on or after the third injection.

If procedures start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first IMP dosing. Procedures will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the procedure stopped prior to the first IMP dosing. If there is clear evidence to suggest that the procedure stopped prior to the first IMP dosing, the procedure will be assumed to be Prior.
Prior and concomitant procedures will be coded according to the MedDRA latest version.
In the FAS, prior and concomitant procedures will be listed by subject and will include the following information: procedures name, SOC, PT, start date, stop date, type of indication (adverse event, medical history, prophylaxis, other) and indication.

6.2.10 Schedule of Activities

Table 10 – 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					

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**
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				

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**
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
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]

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**
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).
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 pre-dose 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.
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 pre-dose and 1 hour post-dose.
n. Injection site reaction assessment should be done pre-dose and approximately 1 hour post-dose, 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.
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 11 – 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

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						
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						

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						
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 pre-dose 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.
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 pre-dose and approximately 1 hour post-dose, 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.
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.

6.3 Appendix 3: Data Handling Conventions

6.3.1 Missing Date Imputation

To account for missing time in date/time when deriving duration variables, the following approaches will be used:

- Time points with unknown start times (where the date is known) will be imputed with a time of 00:00 h or treatment administration time
- Time points with unknown end times (where the date is known) will be imputed with a time of 23:59 h
- Unknown time part will be shown as "-" in listings (meaning not known, missing in source)

6.3.1.1 Missing/Incomplete AE Start Date

Missing / incomplete AE start dates will be printed in listing, unknown part will be shown as "-" in listings (meaning not known, missing in source). Handling of partial AE dates for the sake of determining whether an AE is TEAE are presented in section 4.5.2.

6.3.1.2 Missing/Incomplete AE End Date

Same consideration as presented in section 6.3.1.1.

6.4 Appendix 4: Sample SAS code

In this appendix, examples of SAS codes are provided; these are intended to guide programmers and it is expected these will be adapted in phase of analysis.

6.4.1 Secondary Estimand – ANCOVA sample SAS code is provided as general example and will be adapted in phase of analysis

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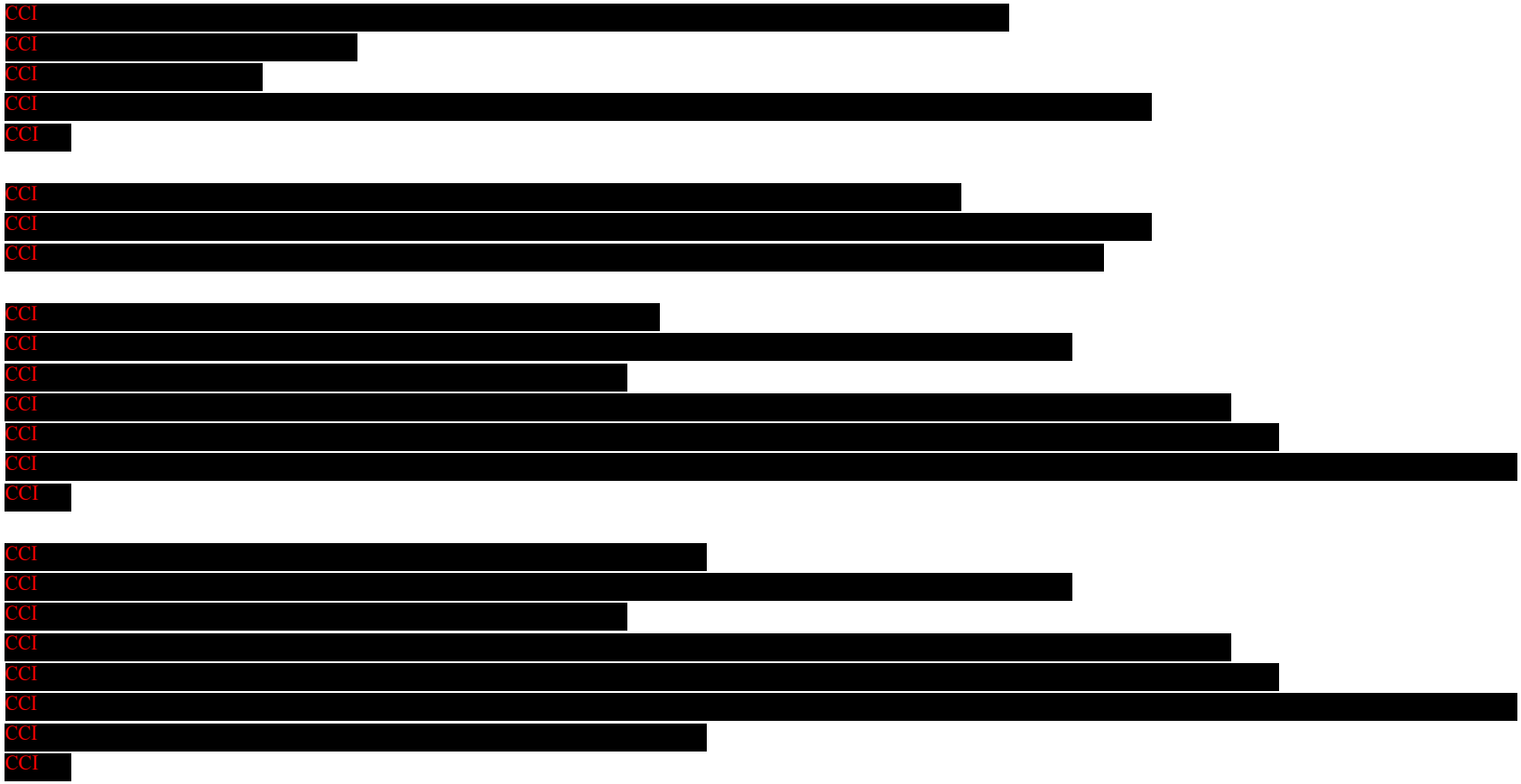
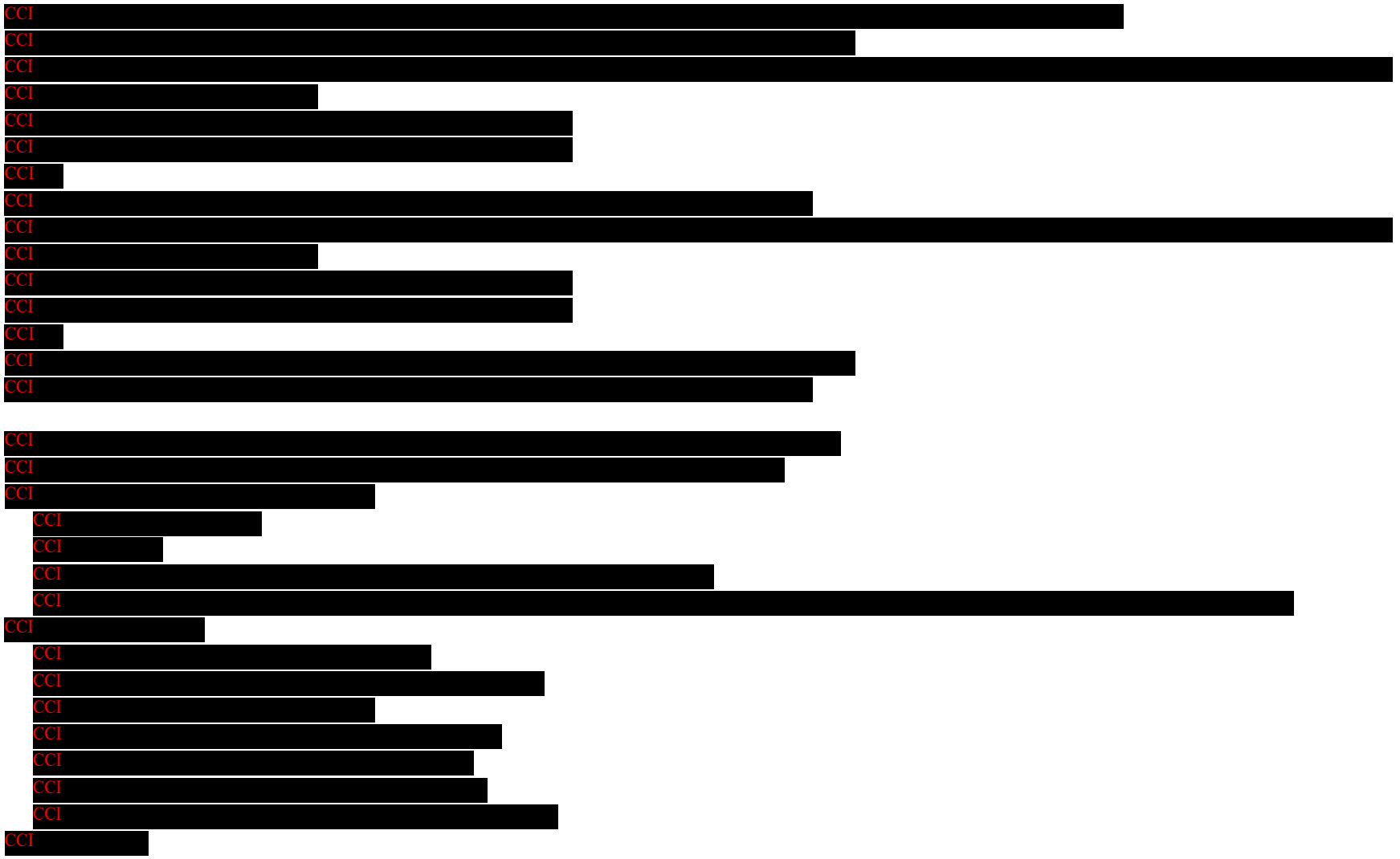
6.4.2 ICE2 Multiple Imputation for EMA – sample SAS code (code is provided as general example and will be adapted in phase of analysis)

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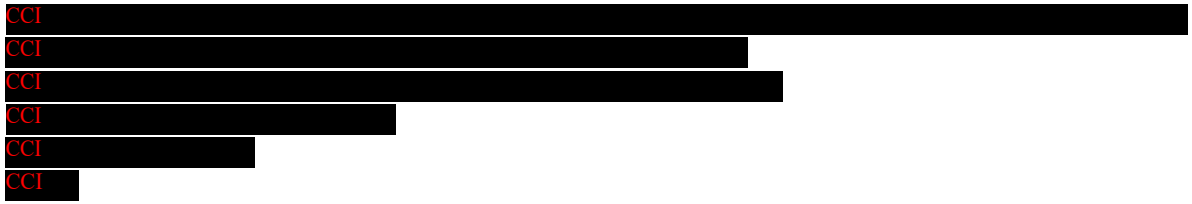
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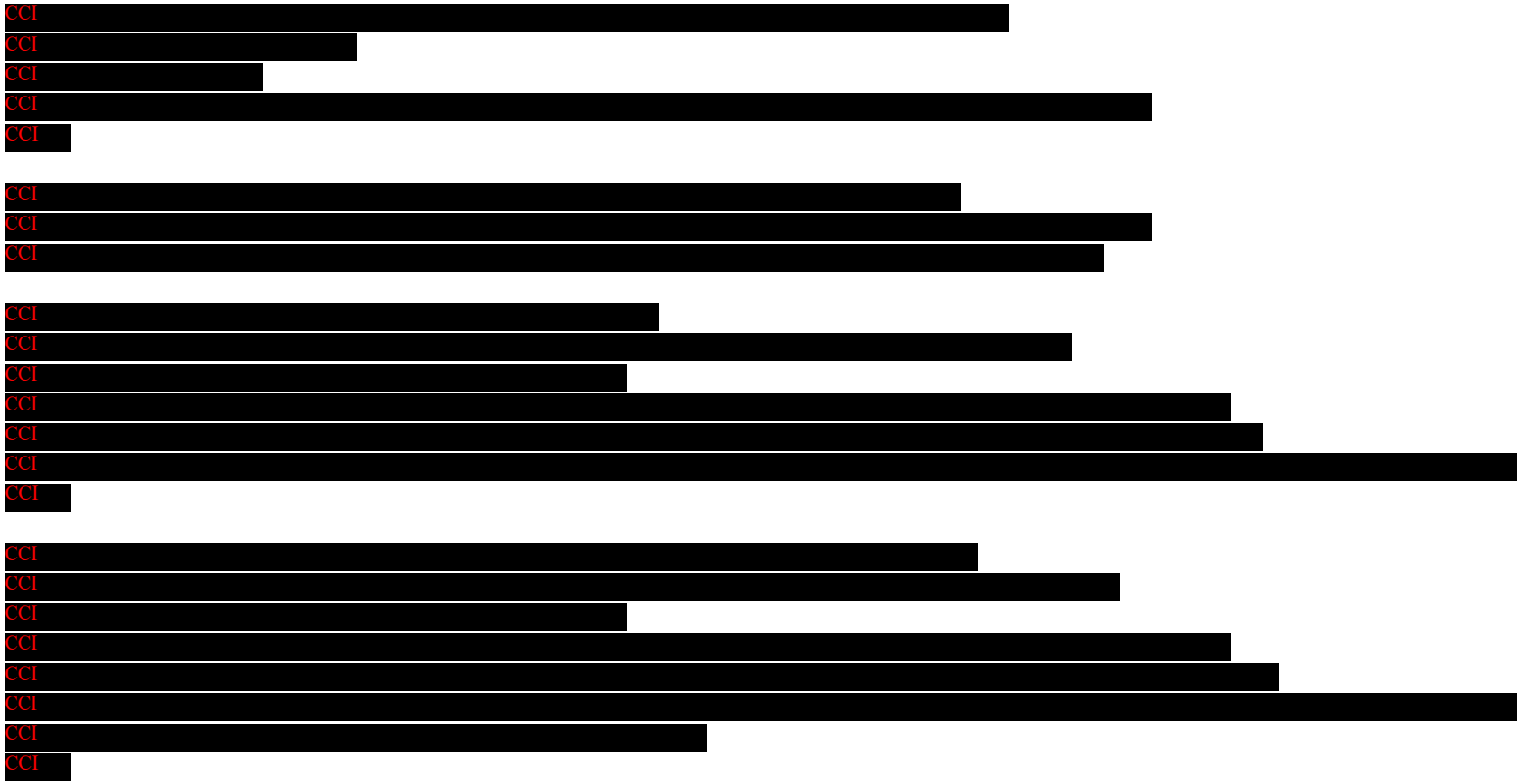
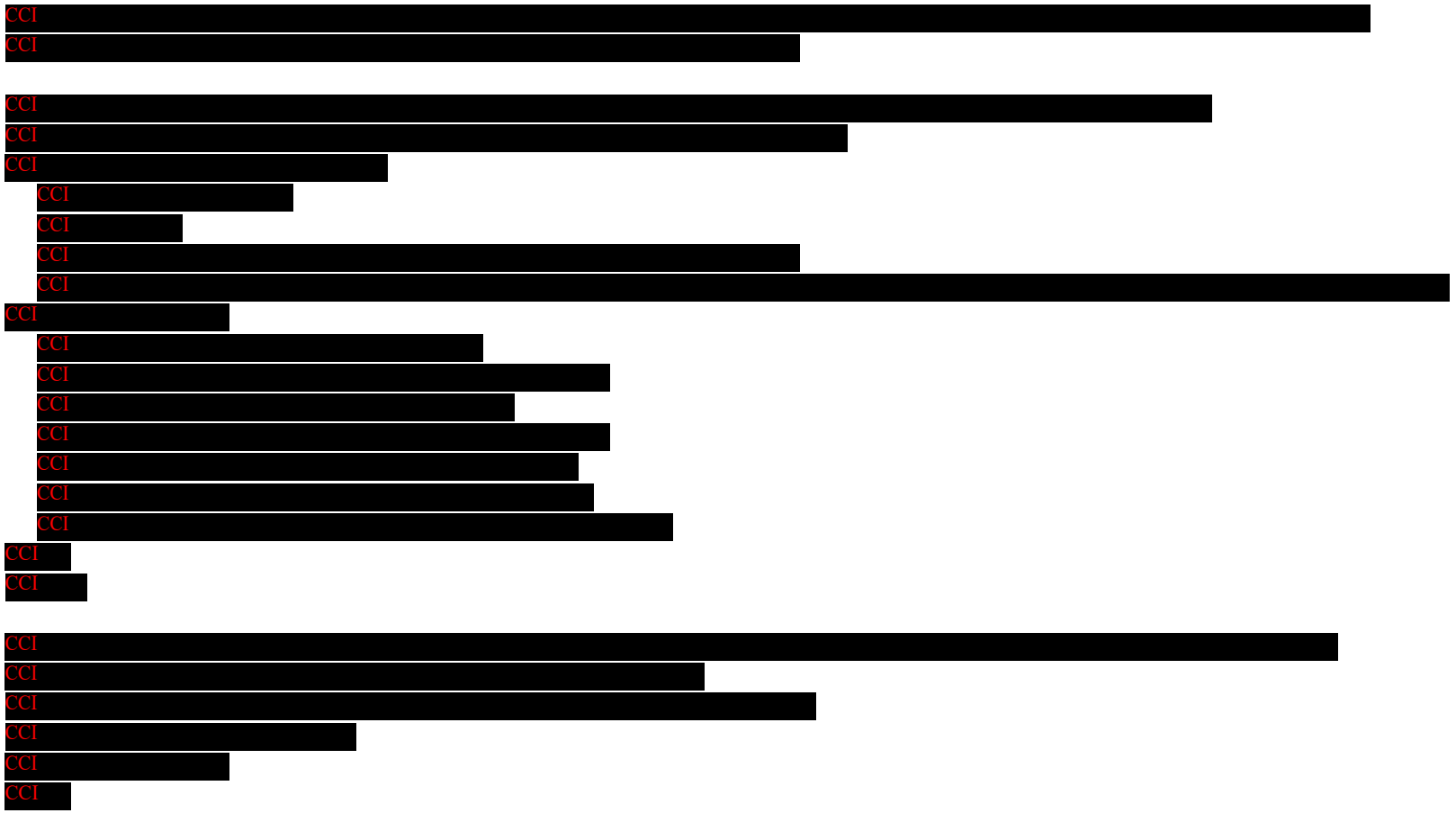
6.4.3 Multiple Imputation for FDA – sample SAS code (code is provided as general example and will be adapted in phase of analysis)

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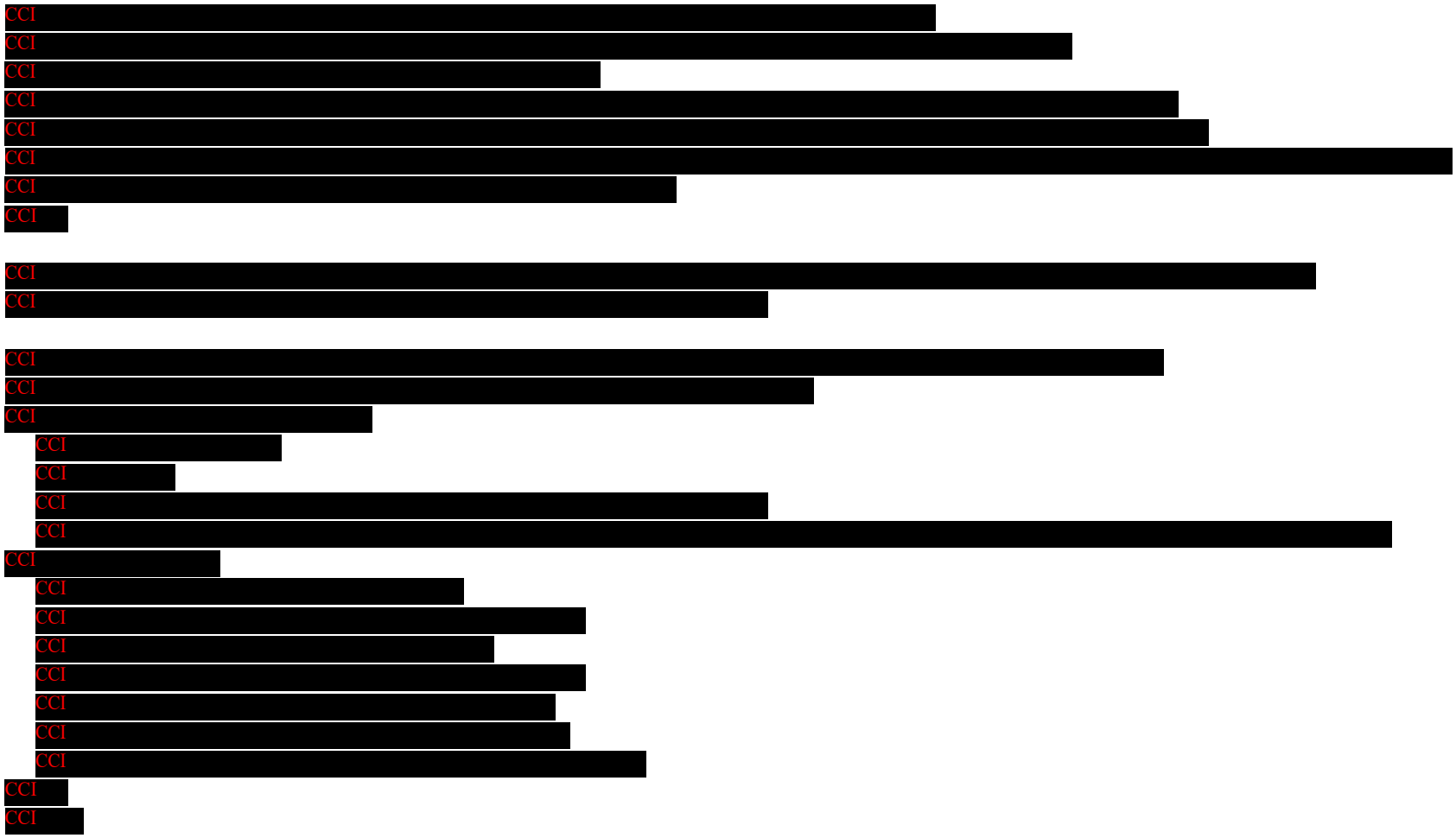
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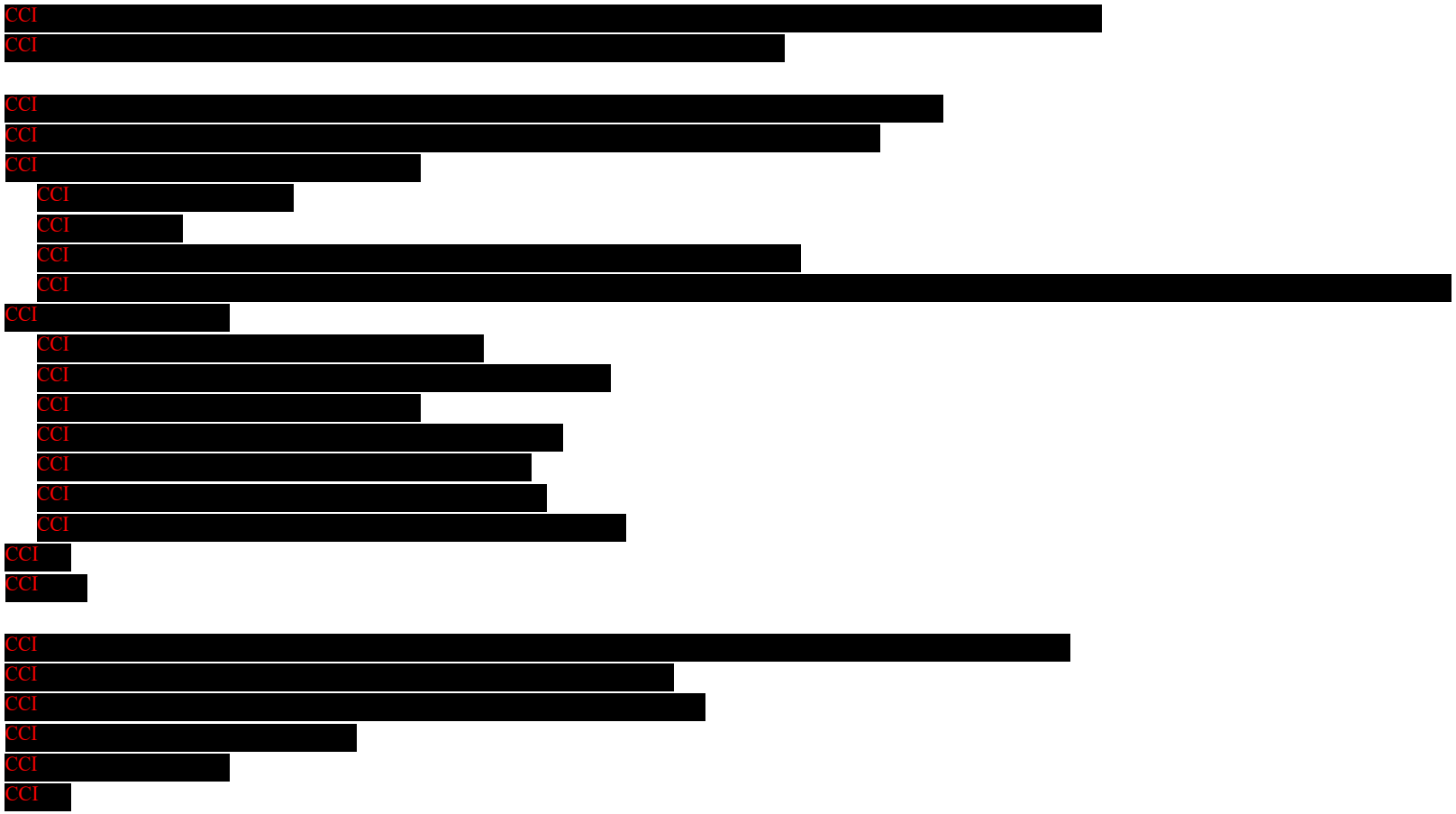
6.4.4 Multiple Imputation for EMA Sensitivity analysis – sample SAS code (code is provided as general example and will be adapted in phase of analysis)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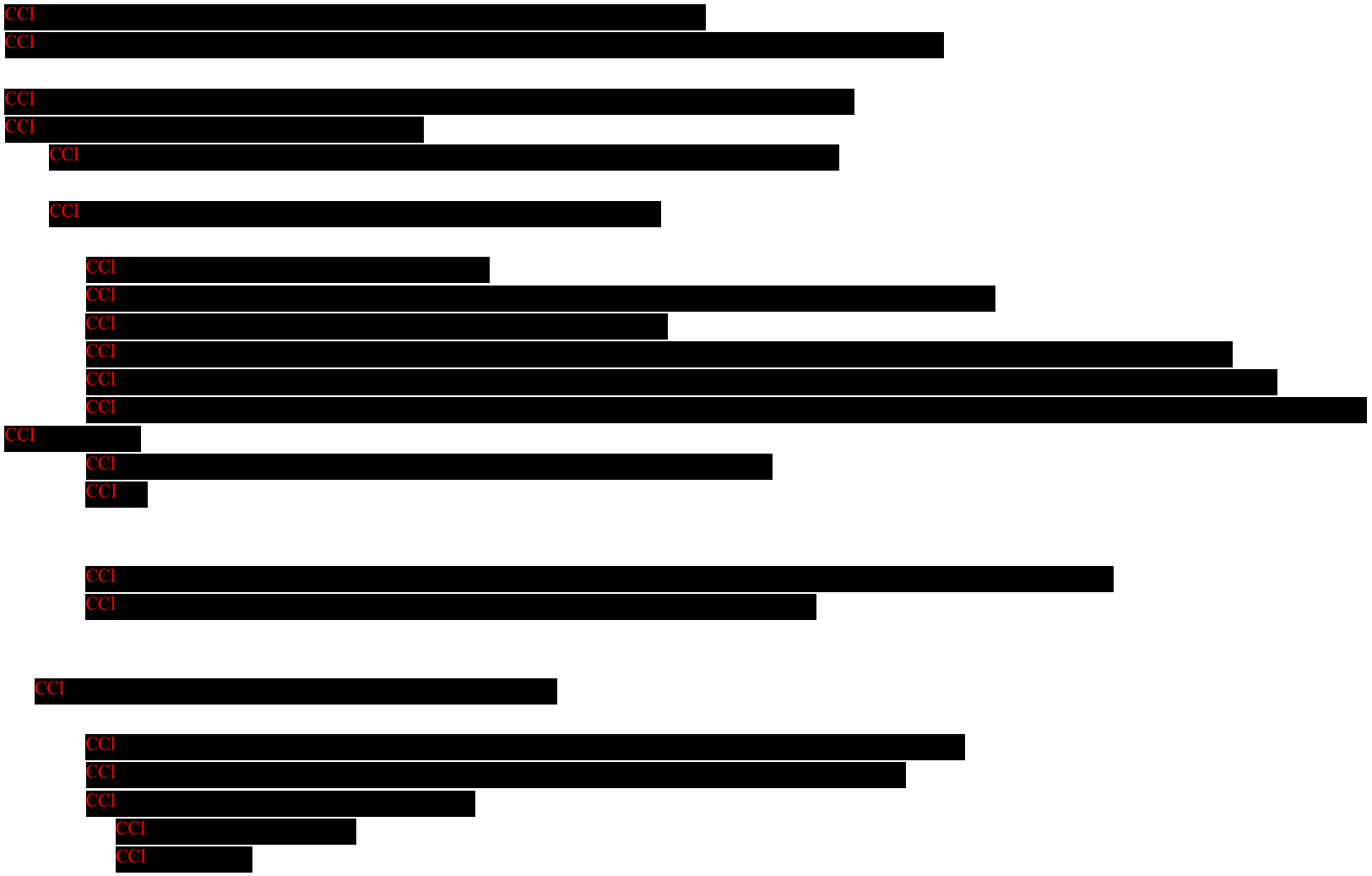
6.4.5 Tipping point for FDA Sensitivity analysis – Approach 1 (code is provided as general example and will be adapted in phase of analysis)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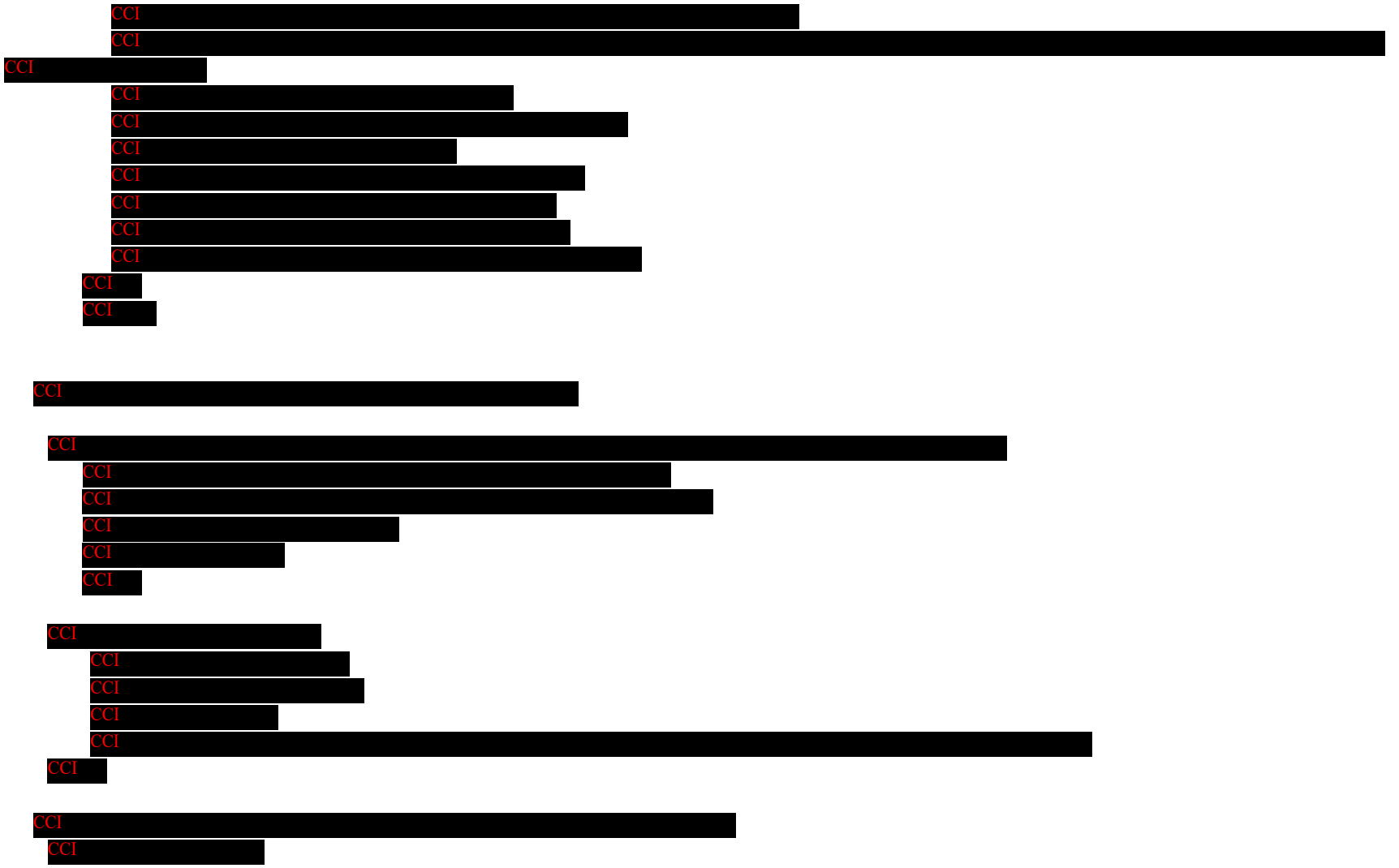
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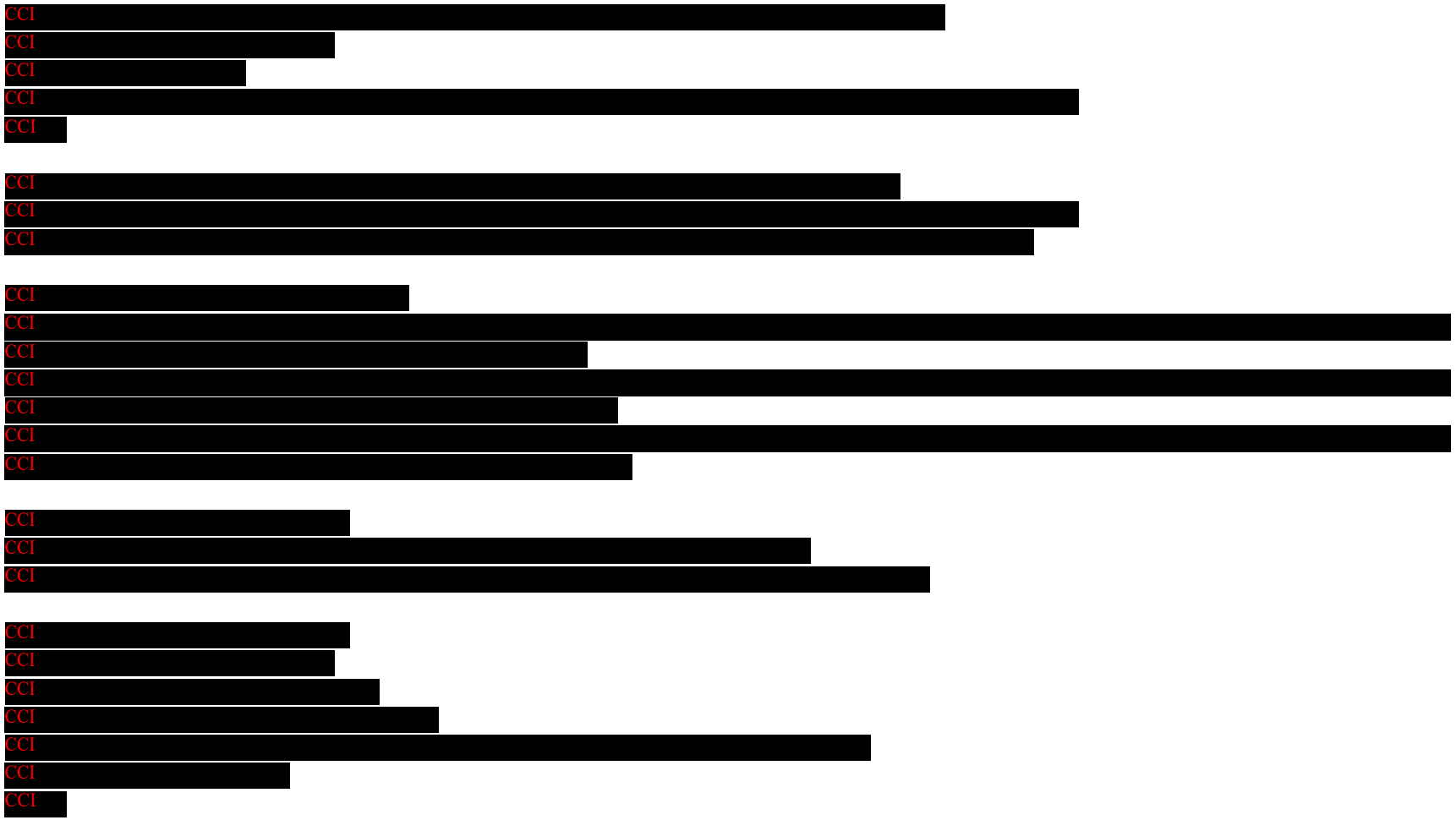
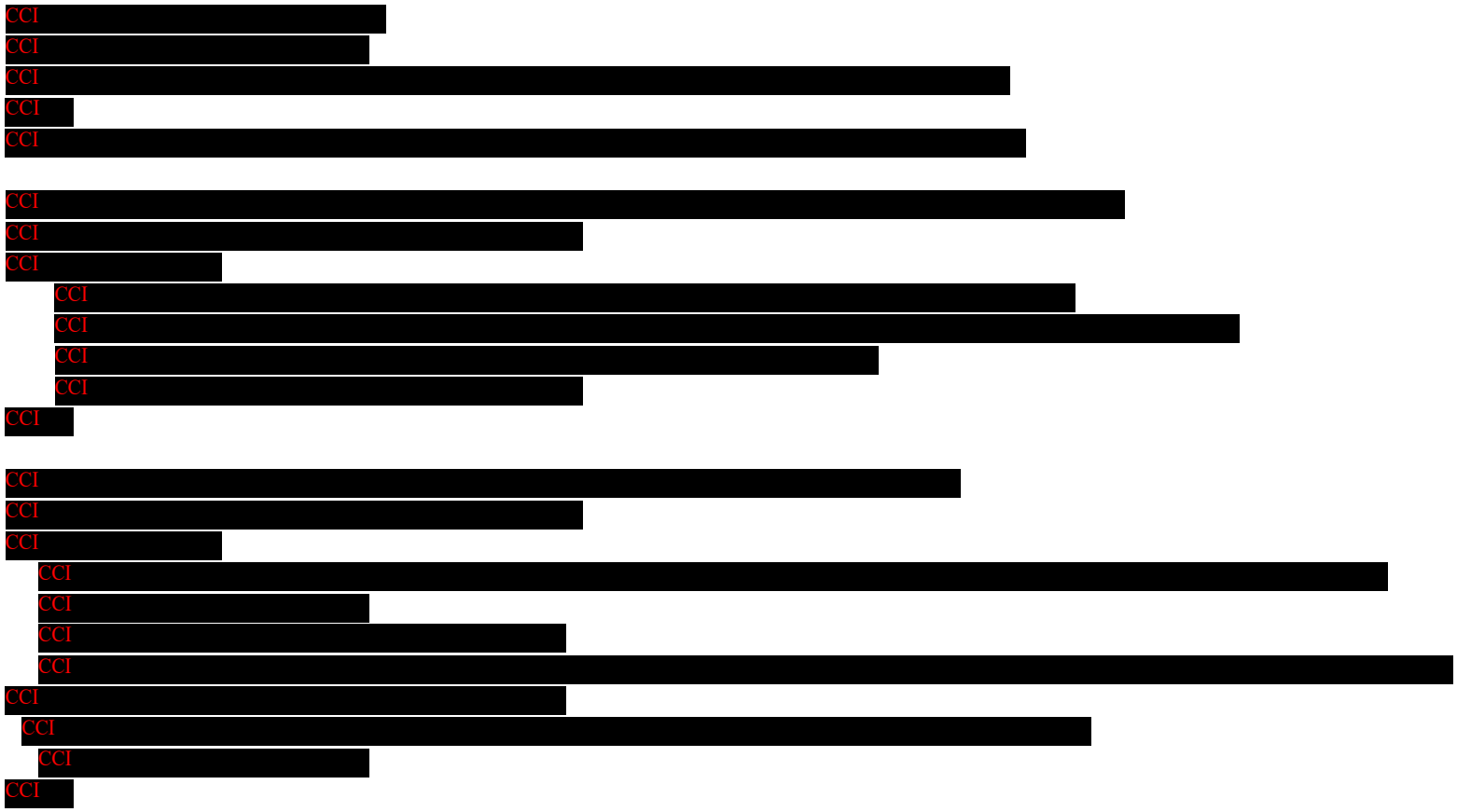
6.4.5.2 Use of macro and plots production (code is provided as general example and will be adapted in phase of analysis)

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6.4.6 Tipping point for FDA Sensitivity analysis – Approach 2 (code is provided as general example and will be adapted in phase of analysis)

6.4.6.1 Macro sample SAS code

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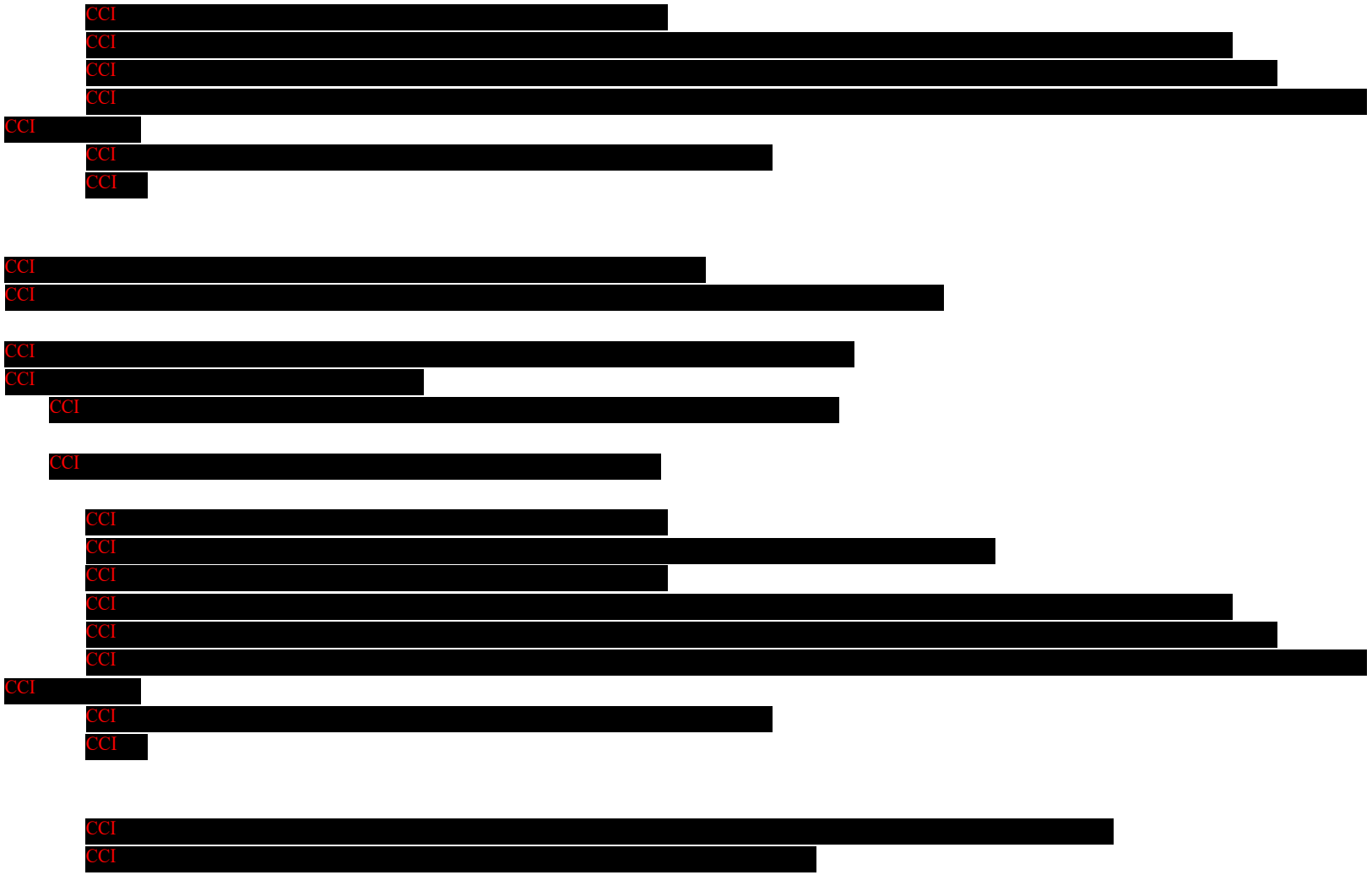
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6.4.6.2 Use of macro and plots production (code is provided as general example and will be adapted in phase of analysis)


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6.4.7 Supplementary Estimand – sample SAS code (code is provided as general example and will be adapted in phase of analysis)

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6.4.8 Derivation of AUEC of %CfB in sCTX from baseline to Week 26 – sample SAS code (code is provided as general example and will be adapted in phase of analysis)

Table 12 contains data for a possible case, with a value of sCTX at each scheduled timepoint up to Week 26.

The piecewise linear function $f(t)f(t)$ for a sample subject is plotted in Figure 5 and the resulting AUEC of sCTX from baseline to Week 26 is highlighted in blue.

Table 12 – sCTX example data

Day	Week	sCTX (ng/mL)	sCTX CfB (ng/mL)	sCTX %CfB	Integral
1	0	0.334	0	0	0
8	1	0.069	0.265	79.341317365	277.69461078
15	2	0.068	0.266	79.640718563	834.13173653
30	4	0.066	0.268	80.239520958	2033.2335329
60	8	0.056	0.278	83.233532934	4485.3293413
90	12	0.082	0.252	75.449101796	6865.5688623
120	17	0.099	0.235	70.359281437	9052.6946108
150	21	0.064	0.27	80.838323353	11320.658683
183	26	0.082	0.252	75.449101796	**AUEC = 13899.401198**

Figure 4 – sCTX example data from baseline up to Week 26

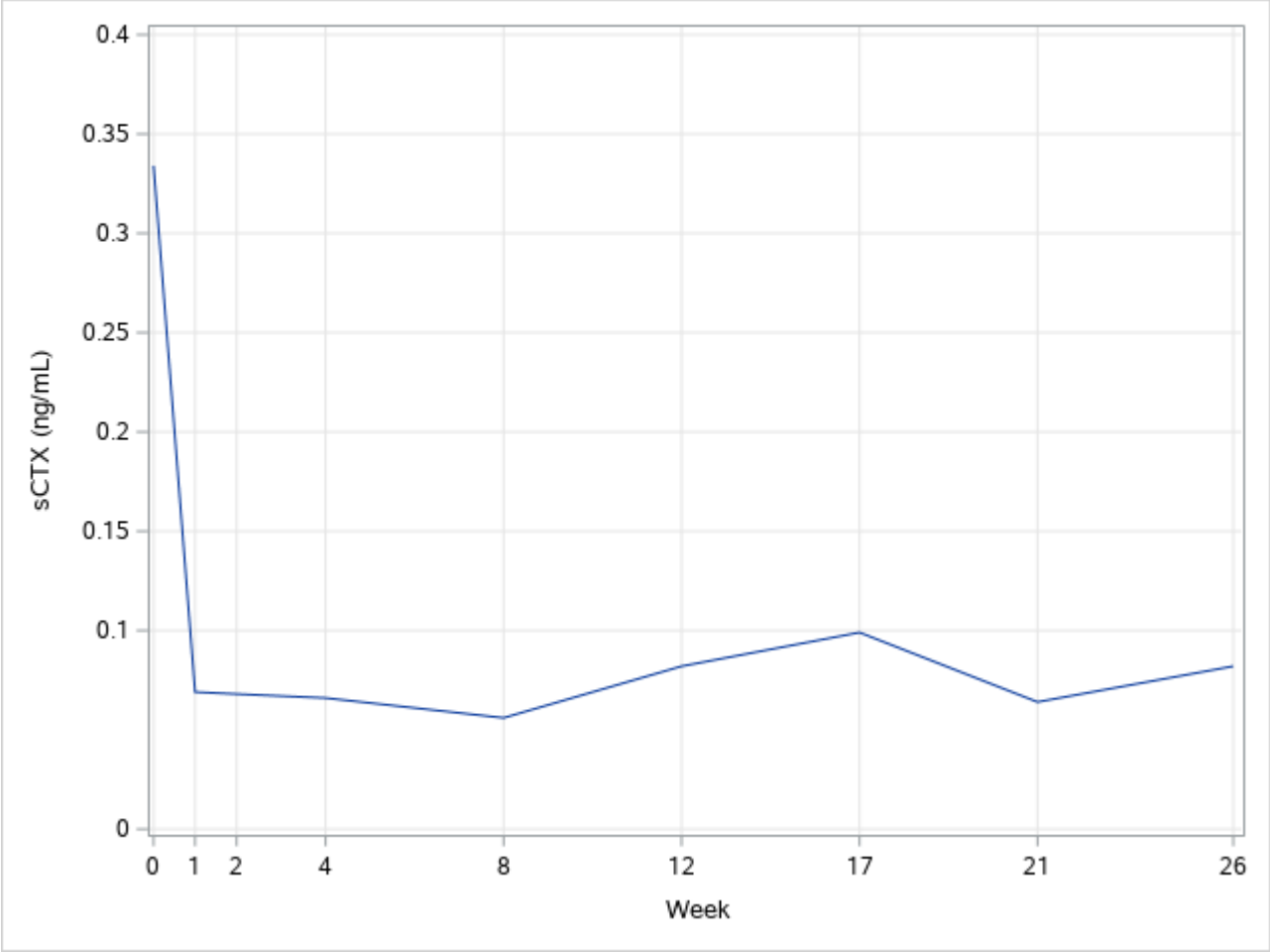
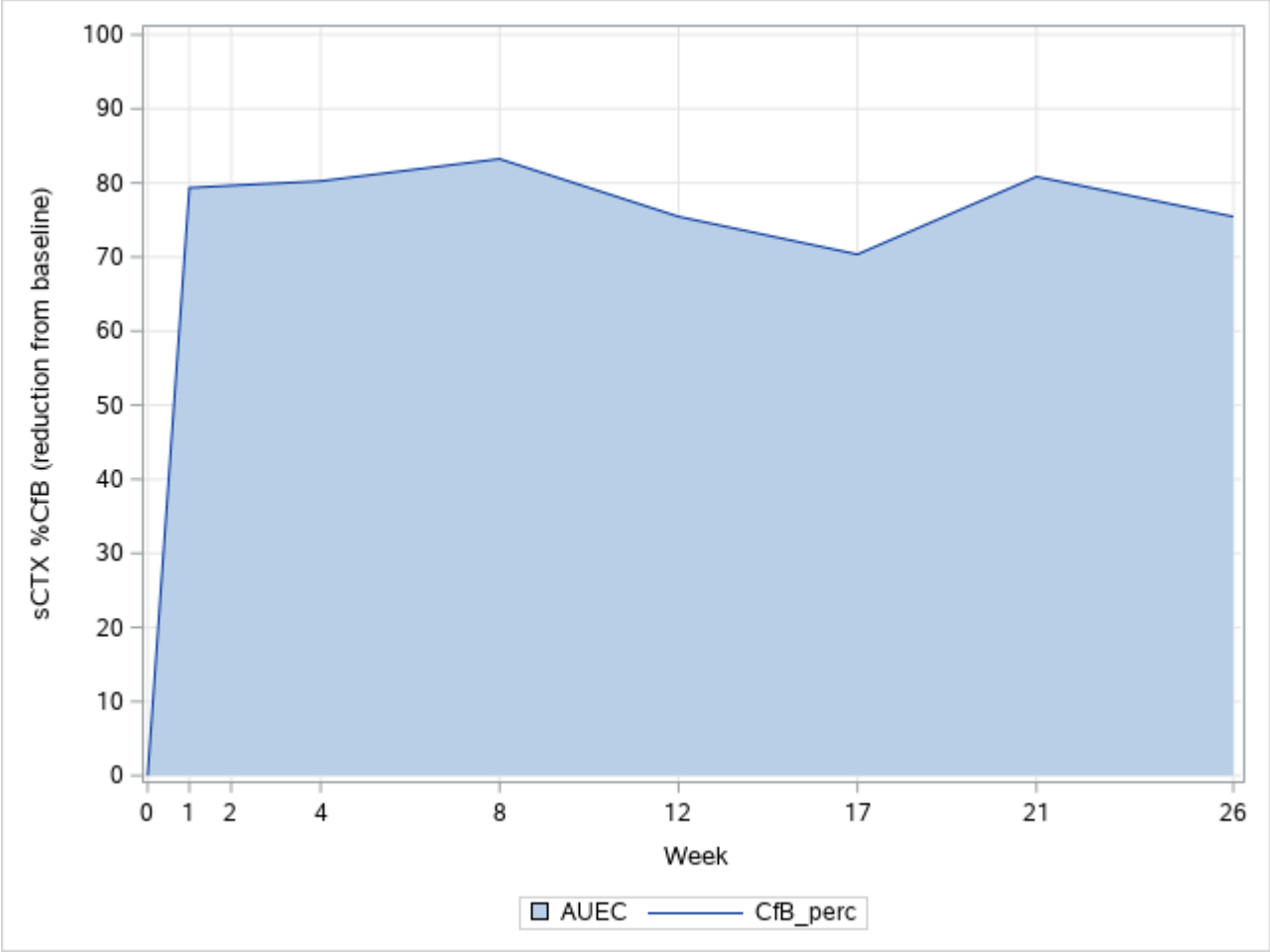
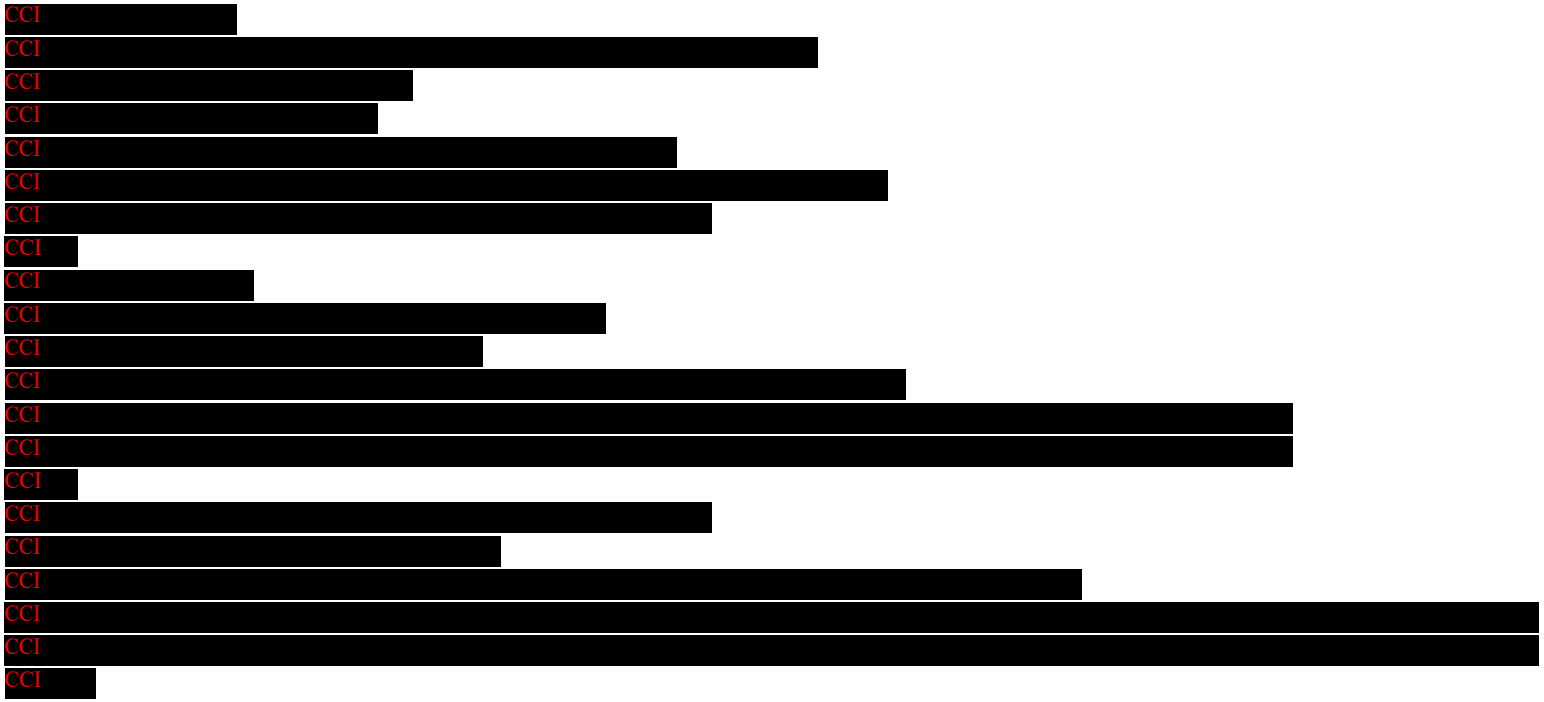


Figure 5 – %CfB AUEC in sCTX example data from baseline up to Week 26



The following SAS example code was utilised to approximate the integral for example data:

6.4.9 Primary Pharmacodynamic Endpoint ANCOVA model and GMR derivation – sample SAS code (code is provided as general example and will be adapted in phase of analysis)



6.4.10 ADA persistent versus transient response – Example cases

Table 13 – ADA persistent versus transient response, in main and transition period – Example cases

Case #	Baseline	Period 1		Period 2				Week 52 Evaluation	Period 3			Week 78 Evaluation
		Week2	Week4	Week26	week28	week30	week52		Week 54	Week 56	Week 78	
1	Negative	Any	Any	Any	Positive	Positive	Positive	**Persistent**	Negative	Negative	Negative	**Persistent**
2	Negative	Any	Any	Any	Positive	Negative	Positive	**Persistent**	Negative	Negative	Negative	**Persistent**
3	Negative	Negative	Negative	Negative	Positive	Negative	Missing	**Persistent**	Missing	Missing	Missing	**Persistent**
4	Negative	Negative	Negative	Negative	Positive	Positive	Missing	**Persistent**	Missing	Missing	Missing	**Persistent**
5	Negative	Negative	Negative	Positive	Missing	Missing	Missing	**Persistent**	Missing	Missing	Missing	**Persistent**
6	Negative	Negative	Negative	Negative	Negative	Negative	Positive	**Persistent**	Negative	Negative	Negative	**Transient**
7	Negative	Positive	Positive	Negative	Negative	Negative	Negative	**Transient**	Positive	Negative	Negative	**Persistent**
8	Negative	Negative	Negative	Negative	Negative	Positive	Negative	**Transient**	Positive	Negative	Negative	**Persistent**
9	Negative	Negative	Negative	Negative	Positive	Negative	Negative	**Transient**	Negative	Positive	Negative	**Persistent**
10	Negative	Negative	positive	Negative	Positive	Negative	Negative	**Persistent**	Negative	Negative	Negative	**Persistent**
11	Negative	Negative	Negative	Negative	Negative	Negative	Positive	**Persistent**	Positive	Negative	Negative	**Transient**
12	Negative	Negative	Negative	Negative	Negative	Negative	Positive	**Persistent**	Positive	Positive	Negative	**Transient**
13	Negative	Negative	Negative	Negative	Negative	Negative	Negative	**Negative**	Negative	Negative	Positive	**Persistent**
14	Negative	Negative	Negative	Negative	Negative	Negative	Negative	**Negative**	Positive	Missing	Missing	**Persistent**
15	Negative	Negative	Negative	Negative	Negative	Negative	Negative	**Negative**	Positive	Negative	Missing	**Persistent**
16	Negative	Negative	Negative	Negative	Negative	Negative	Negative	**Negative**	Positive	Negative	Negative	**Transient**
17	Negative	Negative	Negative	Negative	Negative	Negative	Negative	**Negative**	Negative	Positive	Negative	**Transient**

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Software:

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Approval Signatures

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Gedeon Richter Plc.

RGB-14-101

A Randomised, Double-blind, Multicentre Phase III Study to Assess the Efficacy and Safety ofRGB-14-P Compared to Prolia® in Women with Postmenopausal Osteoporosis

Statistical Analysis Plan Addendum

Parexel Project Number: 252679

SPONSOR SIGNATURE PAGE

Approved by: PPD

PPD

Gedeon Richter Plc.

Approved by: PPD

PPD

Gedeon Richter Plc.

Signatures obtained electronically.

Parexel Signature Page

Signature(s) below confirm that the Statistical Analysis Plan Addendum was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD PPD

TABLE OF CONTENTS

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	Date of last signature	New document
2.0	Date of last signature	Updated to add a section for summary of PK results Updated to add a section for additional summaries of AE and additional AE tables Updated to add a section for summary of medical history and concomitant illness.

1 CHANGES TO THE STATISTICAL ANALYSIS PLAN

1.1 Primary Pharmacodynamic Endpoint – Main Analytical Approach

Section 4.2.2.2 of the statistical analysis plan (SAP) version 1.0 stated that to evaluate the %CfB AUEC sCTX0-m6 (required as primary endpoint for EMA and secondary for FDA), the treatment comparison will be made using the ANCOVA with natural log-transformed AUEC data as the dependent variable while the followings will be model covariates:

- Treatment Arm
- Stratification factors for randomisation:
    - Previous use of bisphosphonates (yes/no)
    - Geographical region (Europe, US)
- Log of baseline sCTX

LS means for %CfB AUEC sCTX0-m6 will be back transformed to derive geometric means and presented with the corresponding LS GMR with their corresponding 95% CIs. Geometric LS mean ratios will be derived by back transforming the LS mean difference between RGB-14-P and Prolia® (RGB-14-P - Prolia®) and presented as ratio (GMR). Back transformed LS mean and GMR will be presented as percentages, as well as the corresponding CIs. Delta method was applied to back transform geometric mean standard error used for the computation of corresponding 95% CIs.

A supplementary analysis will now be performed as followed: To evaluate the %CfB AUEC cSCTX0-m6, the treatment comparison will be made using the ANCOVA with the AUEC data as collected as the dependent variable while the following will be model covariates:

- Treatment Arm
- Stratification factors for randomisation:
    - Previous use of bisphosphonates (yes/no)
    - Geographical region (Europe, US)
- Baseline of sCTX

LS means for %CfB AUEC sCTX0-m6 will be presented with their corresponding 95% confidence intervals (CIs). The LS mean difference between RGB-14-P and Prolia® (RGB-14-P - Prolia®) and the corresponding 95% CI will also be presented.

The change is being made as, although sCTX values are expected to decrease over time following injection, some patients had an increase from baseline in sCTX values (indicated as negative values – see formula in section 4.2.2.1 of SAP version 1.0) and a log-transformation would exclude these data from analysis.

1.2 Primary Efficacy Endpoint – Primary estimand sensitivity tipping point for FDA submission

Two additional tipping point plots will be produced to present the tipping point results of Approach 1 and Approach 2 mention in section 4.2.1.3.2 of the SAP version 1.0.

The first figure will display the sensitivity two-dimensional tipping point multiple imputation – approach 1 – non inferiority and the sensitivity two-dimensional tipping point multiple imputation – approach 2 – non inferiority. The second figure will display the sensitivity two-dimensional tipping point multiple imputation – approach 1 – non superiority and the sensitivity two-dimensional tipping point multiple imputation – approach 2 – non superiority.

For each figure, the horizontal axis will cover the "Shift to RGB" ranging from -7.45 to +7.45, and the vertical axis will cover the "Shift to Prolia" ranging from -7.45 to +7.45.

Claims of non-inferiority/non-superiority met will be displayed by green circles, or red circles otherwise.

The new figures are being produced to assess the tipping points of the of non-inferiority/non-superiority claims more easily.

1.3 Pharmacokinetic Concentrations

Serum concentrations for RGB-14-P and Prolia will be summarised by study day on the full analysis set. The following descriptive statistics will be presented for serum concentrations obtained at each study day: n, number of concentration values below the limit of quantification (nBLQ), (where the lower limit of quantification is defined as 1ng/mL) mean, SD, coefficient of variation (CV%) (calculated as the [standard deviation divided by the mean]*100), geometric mean (calculated as: exp(μ); where μ is the mean of the data on the log transformed values), geometric CV% (calculated as: gCV% =SQRT[exp(s^2) -1]*100; where s is the standard deviation of the log transformed values), minimum, median and maximum.

The following rules will be followed with regards to the number of decimal places/significant figures and presentation of data in tables of concentration data:

- The mean, geometric mean and median will be tabulated to one more decimal place compared to the source data, and the standard deviation (SD) will be tabulated to two more decimal places compared to the source data, but with a maximum of four decimal places.
- Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of four significant digits.

- CV% and gCV% will be presented to one decimal place.

This new table is being produced to support the Listing of serum drug concentration.

1.4 Adverse Events

Section 4.5.2 of the SAP details the summaries to be produced for TEAEs. The following additional summaries will be produced for the overview of the number and percentage of subjects (and number of events) for the TEAEs emerging in the main and transition period for the safety analysis set:

- Any TEAE leading to discontinuation of IMP
- Any treatment related TEAE leading to discontinuation of IMP

A new output will be produced for:

- Number and percentage of subjects for each TEAE leading to discontinuation of IMP categorised by SOC and PT
- Number and percentage of subjects for treatment related TEAE leading to discontinuation of IMP categorised by SOC and PT

The new categories of adverse events and new table are being added to further characterise the safety profile.

1.5 Medical History and Concurrent Illnesses

Section 6.2.6 of the SAP states that medical and surgical history data will be listed. Two additional summary tables will now be produced for medical and surgical history, and concomitant illness.

Medical history is defined as any disease with a start and end date prior to the date of first dose of IMP. Concomitant illness is defined as any disease with an end date on or after the date of the first dose of IMP. Any disease with missing end date and marked as 'Ongoing' will also be considered as concomitant illness.

The following additional summary tables will be produced in the main and transition period for the full analysis set:

- Medical history by SOC and PT
- Concomitant illness by SOC and PT

The new outputs are being added to further characterise the medical history and concomitant illness of the subjects randomised in the study.

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