Sandoz Biopharmaceuticals Clinical Development

GP2411 (INN: denosumab)

Study protocol CGP24112301 / NCT03974100

A randomized, double-blind, multicenter integrated phase I/III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity of GP2411 (proposed biosimilar denosumab) and Prolia® (EU-authorized)

SAP – Detailed Statistical Methodology

Sponsor:	Hexal AG, Industriestr. 25, 83607 Holzkirchen, Germany
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Document History – Changes compared to previous version of the SAP

Version	Date	Changes
1.0	12-Jun-2019	New document
2.0	08-Apr-2020	• Alignment with protocol amendment 5 • Inclusion of table showing number of patients per analysis set • Inclusion of table showing number of patients screened, randomized and treated by site • More detailed fracture specification
3.0	16-Dec-2020	• Alignment with protocol amendment 6 • Lists of protocol deviations leading to exclusion from PPS/PKS/PDS are updated • For protocol deviations relationship to COVID-19 is included • Demographic and baseline characteristics are repeated for the subgroup of patients enrolled pre-COVID and during-COVID • Separate summaries will be provided for concomitant medications (by ATC class and preferred term) and significant non-drug therapies (by SOC and preferred term) • Inclusion of Vitamin D and calcium medications listing (categorization is provided in Appendix based on preferred term) • More detailed sensitivity analysis to assess robustness of normality assumption of MMRM • Guidance for LS-BMD, FN-BMD, TH-BMD values is added, rules for exclusion from analysis are provided • Disclosure requirements for AEs are added • For laboratory evaluation summary statistics are changed to boxplots • Guidance on binding/neutralizing antibodies is added • Inclusion of elapsed time up to Week 26 for drug, CTX and PINP concentrations; rules for exclusion from analysis are provided • Update in Bisphosphonates
4.0	20-Dec-2021	• Lists of protocol deviations leading to exclusion from PPS/PKS/PDS are updated • The 80% confidence interval with a margin of (-2.00%, 2.00%) using the TP1 FAS for Japanese subgroup is specified • The derivation of missing BMD value due to COVID-19 for tipping point analysis is included • Sensitivity analyses excluding patients with ADA positive result in PK analysis set is added. • The source data for BMD parameter is updated • The source data for vertebral fracture is updated • The analysis of vital signs is changed to use the first value • The result of anti-SARS CoV2 antibody testing is included • A stand-alone section 4.7.5 for immunogenicity is updated • Denosumab, CTX and PINP serum concentrations are updated to be listed up to Week 78

Version	Date	Changes
		• The rules for PK and PD parameter derivation are updated • Values below LLOQ and missing data in denosumab, CTX and PINP concentration are moved forward to Section 4.8.2 and Section 4.8.4 • Additional rules of AUEC of %CfB in serum CTX derivation are added and pre-specified • Delete vertebral fracture in Appendix 4 • Delete Appendix 5 & 6 and derive vitamin D, calcium, and bisphosphonates medications by using ATC codes
5.0	01-Feb-2022	• Protocol deviation description of OTH10C updated following update of protocol deviation specification • EXCL25 is dropped from the list of protocol deviations leading to exclusion from PPS/PKS/PDS • Criteria that lead to exclusion of PDS are amended in Section 4.8.4 • Geometric means and CV will be calculated for drug concentration summaries in case there are concentrations <LLOQ • Summary of missing patterns for %CfB in LS-BMD up to Week 52 is added • Impact of immunogenicity on PK is dropped from this SAP • Forest plots on PK and PD parameters will be done on logarithmic scale • Medical history won't be listed
6.0	11-Feb-2022	• Margin update for EMA requirement for primary endpoint %CfB in LS-BMD at Week 52 from 2.00% to 1.45% • EXCL05 is dropped from the list of protocol deviations leading to exclusion from PPS/PDS • For EXCL15 leading to exclusion from PPS/PDS condition similar to EXCL15P5 is added • More details provided on AUEC calculation • Fracture categorization is updated in Appendix 4
7.0	09-May-2022	• The analysis of vital signs is updated to use the average value again as originally proposed • Listing for abnormal vital signs values expanded • Source for pandemic start dates added • Exclusion rule for extreme outliers added to laboratory boxplots of ALT/AST/ALP for better readability • Geometric mean and geometric CV% derivation removed for percent change from baseline calculation of CTX and PINP concentrations which are mainly negative • Removed presentation of lower SD whiskers from graphs where mean-SD <0 for PK concentrations and mean-SD <100% presentation of %CfB in CTX/PINP concentrations as biologically these are implausible • For summary of PD parameter: number of values >0 added

Version	Date	Changes
		• Clarification added for presentation of PK concentration values of 0 on semi-log scale • Coding dictionary versions updated • AE table by SOC and PT with 3% threshold added • Listing of tables from TP1 interim analysis to be rerun added with rationale

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List of abbreviations

%CfB	Percent change from baseline
ADA	Anti-drug antibody
AE	Adverse event
AN(C)OVA	Analysis Of (Co-)Variance
ATC	Anatomical therapeutic chemical
AUCinf	Area under the serum concentration-time curve extrapolated to infinity
AUEC	Area Under the Effect Curve
CfB	Change from baseline
CI	Confidence interval
Clast	Observed last measurable serum concentration
Cmax	Maximum serum concentration (of a drug)
CRO	Clinical Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTX	C-telopeptide
CV% mean	Coefficient of variation (%)
CV% geometric mean	Geometric coefficient of variation (%)
DXA	Dual energy X-ray Absorptiometry
ECG	Electrocardiogram
eCRS	electronic Case Retrieval Strategy
FAS	Full Analysis Set
FN-BMD	Femoral neck-bone mineral density
HA	Health authority
HLT	High level term
IQC	Instrument Quality Control
IRT	Interactive Response Technology
ISR	Injection Site Reaction
Lambda_z	Terminal elimination rate constant
LLOQ	Lower Limit of Quantification
LS-BMD	Lumbar spine-bone mineral density
MAR	Missing at random
MNAR	Missing not at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
PD	Pharmacodynamics
PDS	Pharmacodynamics Analysis Set
PINP	Procollagen I N-terminal propeptide
PK	Pharmacokinetics
PKS	Pharmacokinetics Analysis Set
PPS	Per-Protocol Set
PT	Preferred Term
RAS	Randomized Analysis Set

SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical Analysis Plan
s.c.	subcutaneous
SD	Standard deviation
SOC	System Organ Class
SP	Screening Period
T1/2	Apparent terminal half-life
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures and Listings
TH-BMD	Total hip-bone mineral density
Tmax	The time to reach maximum concentration
TP1	Treatment Period 1
TP2	Treatment Period 2
X-cal	Instrument Cross-calibration

1 Introduction

Study CGP24112301 is an international, multicenter, randomized, double-blind, two-arm, parallel-group study with a total duration of up to 83 weeks. The purpose of this study is to demonstrate similar efficacy, pharmacodynamics (PD), pharmacokinetics (PK), safety, and immunogenicity of GP2411 and Prolia for up to 52 weeks (Treatment Period 1, TP1) in postmenopausal women with osteoporosis, following two 60 mg subcutaneous injections every 6 months.

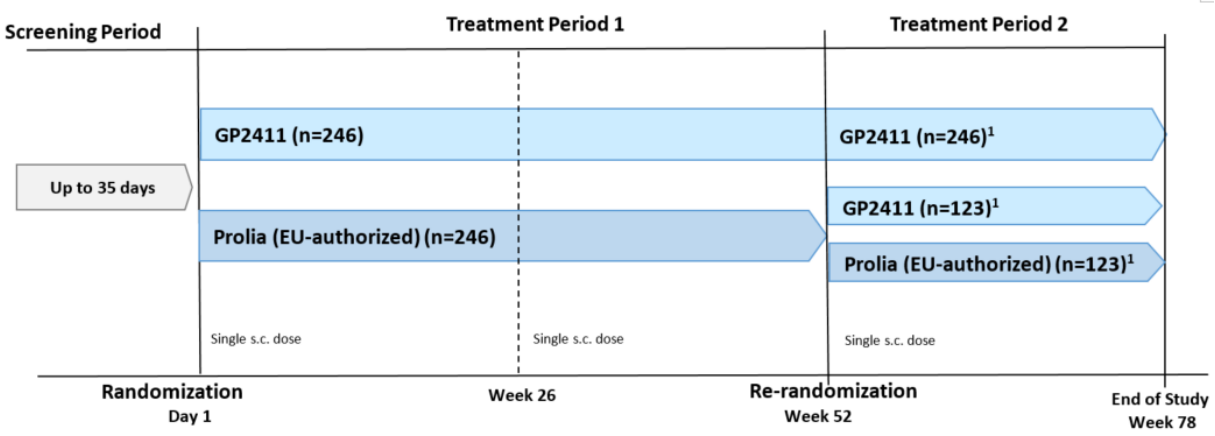
In Treatment Period (TP2), the study also involves a transition from Prolia to GP2411 expected for half of the patients on Prolia at Week 52, with a subsequent evaluation of safety and immunogenicity over the 26 weeks after the transition. All patients treated with GP2411 in Treatment Period (TP1) will continue with GP2411 in TP2.

This statistical analysis plan (SAP) describes in detail the planned analyses and presentation of the results for this study. A detailed description of the planned Tables, Figures and Listings (TFLs) to be presented in the Clinical Study Report (CSR) will be provided in an accompanying TFL shell document.

Any deviations from this SAP with rationale will be described in the CSR.

An initial Screening Period (SP) will be followed by two treatment periods: TP1 from Day 1 up to Week 52; and TP2 from Week 52 to Week 78 (see Figure 1-1). Approximately 492 women with postmenopausal osteoporosis were planned to be randomized on Day 1 of TP1 in a 1:1 ratio into one of two treatment groups: GP2411 or Prolia. At Week 52, all patients still in the trial allocated to the Prolia group in TP1 will be randomized 1:1 to either GP2411 or Prolia for TP2. Patients allocated to GP2411 in TP1 will all continue on GP2411 in TP2. Patients in TP2 will therefore be assigned in an approximate 2:1:1 ratio into three groups: “GP2411/GP2411”, “Prolia/GP2411” or “Prolia/Prolia”.

Figure 1-1 Study design



Data analyses will be performed at two points:

- Interim analysis at Week 52: This will be carried out for all patients have completed Week 52 or discontinued prior to Week 52. In addition, the interim analysis will also

include all available safety data up to Treatment Period 2 which have been collected until the partial database lock.

- Final analysis at Week 78: This will be carried out for all patients who have completed the study.

The interim analysis will allow for an early conclusive read-out of the primary endpoint analyses (see Section 4.10 for details).

Study assessments to be performed at each visit are described in Appendix 1.

2 Statistical and analytical plans

Data will be analyzed by the Sandoz Biostatistics department according to the data analysis Section 12 of the study protocol. Detailed documentation of concluding statistical analyses will be provided, as applicable, in Appendix 16.1.9 of the CSR.

2.1 Study documents and general considerations

The analyses described are based on the Clinical Study Protocol (CSP) Version 06 (Amendment 6) released 30-Oct-2020.

PK and PD parameters will be derived using the computer program Phoenix WinNonlin (version 8.0 or higher).

All other statistical analysis will be performed using SAS® (SAS Institute, Cary NC, USA, version 9.4 or higher version).

Medical coding will be conducted for Adverse Events (AE) and Medical History using MedDRA version 25.0. Coding for medication and procedures will be performed using WHODrug Global B3 Mar 2022.

2.2 Study objectives

2.2.1 Primary objective

Summarized below are the different co-primary endpoints that have been agreed with EMA, FDA and PMDA (Table 2-1). Requirements for co-primary endpoints differ by health authority (HA), as indicated below. For the purpose of this SAP, all endpoints considered primary for at least one HA will be treated as primary throughout the remainder of this document.

Table 2-1 Primary objectives and related endpoints

Primary objectives	Endpoint(s) for primary objective(s)
To demonstrate similar efficacy between GP2411 and EU-authorized Prolia, in terms of lumbar spine-bone mineral density (LS-BMD)	Percent change from baseline (%CfB) in LS-BMD at Week 52 (FDA, EMA, PMDA)
To demonstrate similar PD between GP2411 and EU-authorized Prolia, in terms of the bone resorption marker collagen type I cross-linked C-telopeptide (CTX)	AUEC after first dose, of %CfB in serum CTX (only EMA)
To demonstrate similar PK between GP2411 and EU-authorized Prolia	Serum PK parameters AUCinf and Cmax after first dose (only PMDA)

2.2.2 Secondary objectives and endpoints

The secondary objectives are to further compare GP2411 (test) with Prolia (reference) with respect to the following criteria:

Table 2-2 Secondary endpoints and related endpoints

Secondary objective(s)	Endpoint(s) for secondary objective(s)
Key secondary objective: To demonstrate similar PD between GP2411 and EU-authorized Prolia, in terms of the bone resorption marker CTX	AUEC after first dose of %CfB in serum CTX (FDA, PMDA)
TP1 (Day 1 − Week 52) To compare GP2411 and EU-authorized Prolia in terms of PK, PD, efficacy, safety, and immunogenicity	• %CfB in BMD: LS-BMD, FN-BMD, TH-BMD at Week 26 • %CfB in BMD: FN-BMD, TH-BMD at Week 52 • PD markers: CTX and procollagen I N-terminal propeptide (PINP) serum concentrations as per visit schedule up to Week 52 • Safety: fractures, vital signs, laboratory safety assessments, injection site reactions, electrocardiogram (ECG), occurrence of adverse events (AEs) and serious AEs up to Week 52 • Immunogenicity: Development of binding and neutralizing anti-drug antibodies (ADAs) up to Week 52 • Serum PK parameters AUCinf and Cmax after first dose (only EMA) • Denosumab serum concentrations as per visit schedule up to Week 52
TP2 (Week 52 - Week 78) To further evaluate and compare GP2411 and EU-authorized Prolia in terms of PK, PD, efficacy, safety and immunogenicity, after transitioning 50% of patients on Prolia to GP2411	• %CfB in LS-BMD, FN-BMD, TH-BMD at Week 78 • PD markers: CTX and PINP serum concentrations as per visit schedule from Week 52 up to Week 78 • Safety: fractures, vital signs, laboratory safety assessments, injection site reactions, ECG, occurrence of AEs and serious AEs from Week 52 up to Week 78 • Immunogenicity: Development of binding and neutralizing ADAs from Week 52 up to Week 78 • Denosumab serum concentrations as per visit schedule from Week 52 up to Week 78

2.3 Statistical methods planned in the protocol

The planned analyses are described in Section 12 of the protocol and further detailed in this SAP.

Because of different health authority requirements, there are three sets of primary endpoints in this study:

Table 2-3 List of primary endpoints

Health Authority	Endpoint	Equivalence criteria	Analysis set
EMA	%CfB in LS-BMD at Week 52	95% CI for difference in means contained in [-1.45%, 1.45%]	PPS
	AUEC of %CfB in serum CTX after first dose	95% CI for ratio of geometric means contained in [0.80, 1.25]	PDS
FDA	%CfB in LS-BMD at Week 52	95% CI for difference in means contained in [-1.45%, 1.45%]	TP1 FAS
PMDA	%CfB in LS-BMD at Week 52	95% CI for difference in means contained in [-2.00%, 2.00%]	TP1 FAS
	Serum PK parameter AUCinf after first dose	90% CI for ratio of geometric means contained in [0.80, 1.25]	PKS
	Serum PK parameter Cmax after first dose	90% CI for ratio of geometric means contained in [0.80, 1.25]	PKS

In addition, equivalence testing will also be performed for the following secondary endpoints:

Table 2-4 List of secondary endpoints with equivalence testing

Health Authority	Endpoint	Equivalence criteria	Analysis set
FDA	AUEC of %CfB in serum CTX after first dose	90% CI for ratio of geometric means contained in [0.80, 1.25]	PDS
PMDA	AUEC of %CfB in serum CTX after first dose	95% CI for ratio of geometric means contained in [0.80, 1.25]	PDS

The primary endpoint section describes all endpoints considered primary for at least 1 of the 3 health authorities; the same endpoint(s) may again be referenced as secondary endpoint(s), according to the agreements with the different health authorities.

2.4 Determination of sample size

The required sample size was calculated to simultaneously meet all of the four co-primary endpoints (i.e., testing six hypotheses, see Table 2-3). The predefined equivalence margins were agreed with FDA, EMA and PMDA as being appropriate.

2.4.1 Assumptions of sample size calculation

The calculations were based on the following assumptions:

Table 2-5 Assumptions for sample size calculation

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

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

** Correlation between log(AUCinf) and log(Cmax)

For a conservative estimation of power, the correlation between the PK parameters and the PD/efficacy parameters is assumed to be zero, although most likely there is a correlation between PK and PD endpoints which, however, is difficult to estimate a-priori.

The SD for %CfB in LS-BMD by the end of 52 weeks of treatment is estimated as pooled SD over 3 published clinical trials, see Table 2-6.

Table 2-6 %CfB in LS-BMD at 12 months for denosumab 60mg compared to placebo in three published clinical trials

		Denosumab			Placebo		
i	Study	n_{1i}	Sample mean $[x_{1i}]$	Sample SD $[s_{1i}]$	n_{2i}	Sample mean $[x_{2i}]$	Sample SD $[s_{2i}]$
1	FREEDOM (Cummings et al 2009)	232	5.5	3.88	209	0	3.69
2	McClung et al 2006	41	4.6	3.01	40	-0.8	3.04
3	DEFEND (Bone et al 2008)	163	4.5	4.56	163	-0.6	3.9
	Pooled			4.08*			

* calculated as $\sqrt{(\sum_i (n_{1i}-1)s_{1i}^2)/(\sum_i n_{1i}-3)}$

The coefficients of variation (CVs) of the AUCinf, Cmax and AUEC of baseline corrected serum CTX (% change from baseline) were derived from simulations using a published denosumab population PK/PD model by Amgen (Sutjandra et al 2011, Zheng et al 2015) generated from a simulation study based on denosumab data. The correlation between Cmax and AUCinf is an assumption, and the true value of the correlation is likely to be higher. As above, this assumption leads to a conservative estimate of the power.

2.4.2 Margin derivation of %CfB in LS-BMD

Margin derivation is based on the same 3 published clinical trials as for the estimate of SD of %CfB in LS-BMD (see Table 2-6) and has been agreed with FDA, EMA and PMDA. Information used in the meta-analysis to derive the margins are presented in Table 2-7.

Table 2-7 Meta-analysis of treatment effects of denosumab - placebo

i	Study	Mean difference $[x_{di}]$	Variance of mean difference $[v_{di}]$^	Weight $[w_i = 1/v_{di}]$
1	FREEDOM (Cummings et al 2009)	5.5	0.1308	7.6479
2	McClung et al 2006	5.35	0.4519	2.2131
3	DEFEND (Bone et al 2008)	5.1	0.2209	4.5269
	Overall weighted average	5.35*	0.0695**	

^ calculated as $\frac{(n_{1i}-1)s_{1i}^2+(n_{2i}-1)s_{2i}^2}{n_{1i}+n_{2i}-2} \times \left(\frac{1}{n_{1i}}+\frac{1}{n_{2i}}\right)$ with n_{1i}, n_{2i}, s_{1i}, s_{2i} as defined in Table 2-6

* calculated as $\sum_{i=1}^{3} w_i^2 v_{di}/(\sum_{i=1}^{3} w_i)^2 = 1/\sum_{i=1}^{3} w_i$

** calculated as $\sum_{i=1}^{3} w_i v_{di} / \sum_{i=1}^{3} w_i$

Therefore, the point estimate of the difference in treatment effects is 5.35% with 95% CI (4.83%, 5.87%).

The lower bound of the 95% CI is used to justify an appropriate margin:

- A margin of 1.45% retains at least 70% of the minimum treatment effect (FDA and EMA approach).
- A margin of 2.00% retains more than 50% of the minimum treatment effect (PMDA approach).

2.4.3 Combined sample size calculation

Table 2-8 shows the requirements for the combined testing of all co-primary endpoints for FDA, EMA and PMDA. Estimation of variability for each endpoint is shown in Table 2-5.

Table 2-8 Testing specifications for combined requirements

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

[1] The FDA/EMA for %CfB in LS-BMD requirement is more stringent than the PMDA requirement. The PMDA requirement will therefore be automatically met once the FDA/EMA requirement has been met.

[2] The EMA margin has only been updated from (-2.00%, 2.00%) to (-1.45%, 1.45%) after enrollment had been closed. However, the 15% drop-out rate is still valid for exclusion from PPS based on actual drop-out and protocol deviation exclusion rate.

100,000 random samples of sample size of 418 evaluable patients (209 evaluable patients per arm) were generated from a multivariate normal distribution as defined in Table 2-5 leading to a sample size of 492 patients (246 per arm). Using the testing requirements that are defined in Table 2-8, each co-primary endpoint was tested for each random sample. If all four tests were passed, then the sample was an overall success. The overall power was estimated as the percentage of overall successes out of the 100,000 random samples. Using the above simulation, a power of 90.4% was obtained for simultaneously passing all equivalence tests for the co-primary endpoints.

Treatment Period 2

The analysis of the TP2 is only descriptive and therefore no formal sample size calculation is conducted for the TP2.

2.4.4 Supplementary analysis of primary endpoint

With a sample size of 492, assuming a drop-out rate of 25%, the power of the supplementary analysis for %CfB in LS-BMD for PPS using a (-1.45%, 1.45%) margin can be estimated to be

85.0%. However, with the expectation to observe a lower SD for PPS the power might be higher than 85.0%.

2.5 Randomization and stratification

Randomization is stratified into one of 24 strata at enrollment dependent on the following four stratification factors:

- Region (US, Rest of the World, Japan)
- Age group (<65 years/ ≥65 years)
- Prior bisphosphonates use (yes / no)
- Body weight group (<70 kg/ ≥70 kg).

Region is included as an administrative stratification factor in order to ensure a balanced allocation of patients in each region for relevant region-specific subgroup analyses. Prior bisphosphonates use was identified as a potential source of heterogeneity for the primary endpoint of LS-BMD and fracture incidence rates that cannot be assured to be completely controlled through the use of inclusion/exclusion criteria, and hence a prior treatment with bisphosphonates (yes/ no) is included as a stratification factor to balance prior treatment heterogeneity within the selected population in the study. Age was added as stratification factor as fracture incidence rate increases significantly after the age of 65 years with primary endpoint LS-BMD not being a sensitive predictor of fracture rates below the age of 65 years (CHMP 2005, Ettinger et al 2010). Weight is considered a major influencing factor on the PK endpoints.

For each strata combination, a separate randomization list is generated within the Interactive Response Technology (IRT) system using a random permutated block algorithm.

Patients are allocated in a double-blinded manner in the ratio 1:1 to either receive GP2411 or Prolia during TP1 (including two doses with the first dose on Day 1 and the second scheduled at 6 months at Visit 11).

Patients who enter TP2 and received GP2411 in TP1 will continue on GP2411; patients who received Prolia in TP1 are randomized in a 1:1 ratio either to switch to GP2411 or to continue on Prolia in TP2.

Even though unblinding will take place for the interim analysis, study drug in TP2 will be allocated in a double-blind manner. In order to maintain the TP1 blind during TP2, TP2 study drug allocation will be performed using the IRT system. There will be no stratification for randomization in TP2.

2.6 Definitions of analysis sets

The following data sets will be used for analysis of the study data.

In case of stratification errors recorded within the IRT system, patients will be assigned to the strata as collected in the IRT system for the TP1 FAS and to the strata as derived from the values stored in the clinical database for the PPS.

2.6.1 Treatment Period 1 Randomized Analysis Set

The Treatment Period 1 Randomized Analysis Set (TP1 RAS) consists of patients who were randomized into TP1. The TP1 RAS will include any patients who were randomized into TP1 including those that were not treated.

A patient will be included in TP1 RAS if a valid randomization date for TP1 is available.

The TP1 RAS will be used for the description of study disposition in TP1 (see Section 4.2).

2.6.2 Treatment Period 1 Full Analysis Set

The Treatment Period 1 Full Analysis Set (TP1 FAS) is a subset of the TP1 RAS and consists of all patients who were randomized into TP1, who received at least one dose of study medication and for whom at least one post-baseline LS-BMD value (either at Week 26 or Week 52 or at both visits) is available. Patients in this analysis set will be analyzed according to their intended (randomized) treatment and stratification.

The TP1 FAS will be used as primary analysis set for LS-BMD for FDA and PMDA and in a supportive manner for EMA and other efficacy endpoints unless otherwise stated.

2.6.3 Treatment Period 1 Safety Set

The Treatment Period 1 Safety Set (TP1 SAF) consists of all patients who received at least one dose of study medication. Patients will be analyzed according to the study treatment received.

A patient will be included in TP1 SAF if at least one non-missing non-zero dose of study drug of either GP2411 or Prolia is available in TP1.

The TP1 SAF will be used for the analysis of safety data in TP1 (see Sections 4.4 and 4.7.4).

2.6.4 Per-Protocol Set

The Per-Protocol Set (PPS) is a subset of TP1 RAS and is characterized by the following criteria.

- The LS-BMD assessments at baseline and Week 52 are available
- The patient received treatment according to protocol at Day 1 and Week 26
- Patients experienced no relevant protocol deviations (see Table 2-9) which would affect LS-BMD up to Week 52 (the time of the primary analyses)

Relevant protocol deviations leading to exclusion from PPS are defined as follows:

Table 2-9 Protocol deviations leading to exclusion from PPS

Protocol deviation identifier	Protocol deviation term for reporting	Additional criteria
INCL01, INCL01B	Incl crt.1 not met: Signed informed consent must be obtained prior to participation in the study	
INCL02	Incl crt.2 not met: Subject is not confirmed as postmenopausal woman, diagnosed with osteoporosis.	

Protocol deviation identifier	Protocol deviation term for reporting	Additional criteria
INCL03, INCL03B	Incl crt.3 not met: Subject is not aged ≥ 55 and ≤ 80 years at screening	
INCL05	Incl crt.5 not met: Subject absolute bone mineral density consistent with T-score ≤ -2.5 and ≥ -4.0 at the lumbar spine as measured by DXA during the Screening Period	
INCL06	Incl crt.6 not met: At least two vertebrae in the L1-L4 region and at least one hip joint are evaluable by DXA	
EXCL01	Excl crt.1 met: Use of other investigational drugs within 5 half-lives of the drug or until the expected pharmacodynamic effect of the drug has returned to baseline	
EXCL02	Excl crt.2 met: Previous exposure to denosumab (Prolia, Xgeva, or biosimilar denosumab)	
EXCL04	Excl crt.4 met: History and/or presence of one severe or more than two moderate vertebral fractures	
EXCL06	Excl crt. 6 met: Presence of active healing fracture according to assessment of investigators	
EXCL07	Excl crt.7 met: History and/or presence of bone or metabolic disease (except osteoporosis) that may interfere with the interpretation of the results	
EXCL08	Excl crt.8 met: Ongoing use of any osteoporosis treatment (other than calcium and vitamin D supplements)	
EXCL09	Excl crt.9 met: Systemic glucocorticosteroids (≥ 5 mg prednisone equivalent per day for ≥ 10 days or a total cumulative dose of ≥ 50 mg) within the past 3 months before screening	
EXCL10	Excl crt.10 met: Other bone active drugs within the past 3 months before screening	
EXCL12	Excl crt.12 met: Current uncontrolled status of hypothyroidism or hyperthyroidism	
EXCL13	Excl crt.13 met: History and/or current hypoparathyroidism or hyperparathyroidism, irrespective of current controlled or uncontrolled status	
EXCL14	Excl crt.14 met: Vitamin D deficiency (25 [OH] vitamin D serum level < 20 ng/mL). Vitamin D repletion is permitted and patients will be rescreened to re-evaluate Vitamin D level post repletion	
EXCL15	Excl crt.15 met: Current hypocalcemia or hypercalcemia based on albumin adjusted serum calcium	If serum calcium <2.1 mmol/l or >2.62 mmol/l at Screening[2]

Protocol deviation identifier	Protocol deviation term for reporting	Additional criteria
EXCL15P5	Excl crt.15 met: Current hypocalcemia or hypercalcemia based on serum calcium	
EXCL16	Excl crt.16 met: Known intolerance to, or malabsorption of calcium or vitamin D supplements	
EXCL22	Excl crt.22 met: Presence of clinically significant active infections (as per investigator' discretion) that may increase the risk associated with study participation	
EXCL23	Excl crt.23 met: Positive serology indicating Hepatitis B or Hepatitis C infections	
EXCL24	Excl crt.24 met: Positive serology for human immunodeficiency virus (HIV) infection or known diagnosis of AIDS	
WITH01	Subject not withdrawn from study after informed consent was withdrawn	If withdrawn prior to Visit 15
WITH02	Study treatment not discontinued according to the protocol	If prior to Visit 11
TRT01	Subject is dosed with expired IP	If Visit 2 or 11
TRT02	Subject is dosed with damaged IP	If Visit 2 or 11
TRT03	Incorrect IP (other than assigned by randomization) given to the subject	If Visit 2 or 11
TRT06	Any deviation from dose or regimen of IP leading to risks for subjects' safety or data integrity	If Visit 2 or 11
TRT07	Subject is dosed with IP rejected for use following temperature deviation	If Visit 2 or 11
TRT08	Unblinding in error	If before Visit 15
COMD02	Prohibited medication used	If before Visit 15
OTH10C [1]	Lumbar spine BMD (DXA scan) performed more than 14 days after date of dosing	If Visit 15
OTH11	Relevant medical history, previous and/or current medications not recorded	
OTH13	DXA scan performed outside of allowed time limit	If screening

[1] Calyx, the central imaging vendor for study CGP24112301, recommended that a 14 days interval after dosing for DXA scan acquisition is the appropriate range for the per-protocol analysis. This recommendation was based on the following reasons: (1) In post-menopausal women due to loss of estrogen, the concentration of RANKL (denosumab's target) increases thereby also increasing osteoclastogenesis and resultant increase in bone resorption which outstrips the rate of bone formation at the tissue level. Inhibition of RANKL by denosumab leads then again to enhanced bone formation. The time needed for bone formation followed by mineralization of the bone at resorbed sites usually takes months (Dempster et al. 2012). (2) An interval of 14 days is in line with the minimally acceptable precision of DXA measurements (International Society of Clinical Densitometry 2019 Official Position Adult).

[2] Consistent with exclusion criterion 15 as it was introduced in Protocol v5.0 and captured thereafter in EXCL15P5

Protocol deviations listed in Table 2-9 above lead to exclusion from PPS. Protocol deviations leading to exclusion from other analysis sets are defined below (see Sections 2.6.5 and 2.6.6).

Specifically, it is not necessary for the patient to have received the second dose at Week 26 per protocol in order to be included in the PDS or PKS. However, it is necessary in order for a patient to belong to the PPS. The criteria to qualify a protocol deviation as leading to exclusion from each analysis set will be updated on an ongoing basis. However, the final criteria will be assessed and incorporated into the SAP version finalized before partial database lock for the interim analysis. The PPS will be the analysis set used for the efficacy analyses including the primary endpoint of LS-BMD for EMA (see Sections 4.6 and 4.7.1).

2.6.5 PD Analysis Set

The Pharmacodynamics Analysis Set (PDS) is a subset of TP1 RAS and is characterized by the following criteria:

- CTX values are available in order to be able to calculate the AUEC value for the primary analysis (see Section 4.8.4)
- The patients received treatment according to protocol at Day 1
- They experienced no relevant protocol deviations (see Table 2-10) which would affect CTX measurements up to Week 26 (the time of the primary analyses)

Table 2-10 Protocol deviations leading to exclusion from PDS

Protocol deviation identifier	Protocol deviation term for reporting	Additional criteria
INCL01, INCL01B	Incl crt.1 not met: Signed informed consent must be obtained prior to participation in the study	
INCL02	Incl crt.2 not met: Subject is not confirmed as postmenopausal woman, diagnosed with osteoporosis.	
INCL03, INCL03B	Incl crt.3 not met: Subject is not aged ≥ 55 and ≤ 80 years at screening	
EXCL01	Excl crt.1 met: Use of other investigational drugs within 5 half-lives of the drug or until the expected pharmacodynamic effect of the drug has returned to baseline	
EXCL02	Excl crt.2 met: Previous exposure to denosumab (Prolia, Xgeva, or biosimilar denosumab)	
EXCL04	Excl crt.4 met: History and/or presence of one severe or more than two moderate vertebral fractures	
EXCL06	Excl crt. 6 met: Presence of active healing fracture according to assessment of investigators	
EXCL07	Excl crt.7 met: History and/or presence of bone or metabolic disease (except osteoporosis) that may interfere with the interpretation of the results	
EXCL08	Excl crt.8 met: Ongoing use of any osteoporosis treatment (other than calcium and vitamin D supplements)	
EXCL09	Excl crt.9 met: Systemic glucocorticosteroids (≥ 5 mg prednisone equivalent per day for ≥ 10 days or	

Protocol deviation identifier	Protocol deviation term for reporting	Additional criteria
	a total cumulative dose of ≥ 50 mg) within the past 3 months before screening	
EXCL10	Excl crt.10 met: Other bone active drugs within the past 3 months before screening	
EXCL12	Excl crt.12 met: Current uncontrolled status of hypothyroidism or hyperthyroidism	
EXCL13	Excl crt.13 met: History and/or current hypoparathyroidism or hyperparathyroidism, irrespective of current controlled or uncontrolled status	
EXCL14	Excl crt.14 met: Vitamin D deficiency (25 [OH] vitamin D serum level < 20 ng/mL). Vitamin D repletion is permitted and patients will be rescreened to re-evaluate Vitamin D level post repletion	
EXCL15	Excl crt.15 met: Current hypocalcemia or hypercalcemia based on albumin adjusted serum calcium	If serum calcium <2.1 mmol/l or >2.62 mmol/l on Screening visit[1]
EXCL15P5	Excl crt.15 met: Current hypocalcemia or hypercalcemia based on serum calcium	
EXCL23	Excl crt.23 met: Positive serology indicating Hepatitis B or Hepatitis C infections	
EXCL24	Excl crt.24 met: Positive serology for human immunodeficiency virus (HIV) infection or known diagnosis of AIDS	
WITH01	Subject not withdrawn from study after informed consent was withdrawn	If withdrawn prior to Visit 11
TRT01	Subject is dosed with expired IP	If Visit 2
TRT02	Subject is dosed with damaged IP	If Visit 2
TRT06	Any deviation from dose or regimen of IP leading to risks for subjects' safety or data integrity	If Visit 2
TRT07	Subject is dosed with IP rejected for use following temperature deviation	If Visit 2
COMD02	Prohibited medication used	If before Visit 11

[1] Consistent with exclusion criterion 15 as it was introduced in Protocol v5.0 and captured thereafter in EXCL15P5

The PDS will be the analysis set used for the PD analyses of CTX and PINP related endpoints (see Sections 4.6.2.2, 4.7.2 and 4.8.3). The reasons for exclusion from PDS, including exclusion flags as defined in Section 4.8.4, will be summarized by number and percentages. Patients will be analyzed according to the study treatment received.

2.6.6 PK analysis Set

The PK Analysis Set (PKS) is a subset of the TP1 RAS and is characterized by the following criteria:

- At least one PK primary endpoint (Cmax and AUCinf) is evaluable (see Section 4.8.2)

- The patients received treatment according to protocol on Day 1
- They experienced no relevant protocol deviations (see Table 2-11) affecting the PK parameters up to Week 26 (the time of the primary analyses)

Relevant protocol deviations leading to exclusion from PKS are defined as follows:

Table 2-11 Protocol deviations leading to exclusion from PK

Protocol deviation identifier	Protocol deviation term for reporting	Additional criteria
INCL01, INCL01B	Incl crt.1 not met: Signed informed consent must be obtained prior to participation in the study	
INCL02	Incl crt.2 not met: Subject is not confirmed as postmenopausal woman, diagnosed with osteoporosis.	
INCL04, INCL04B	Incl crt.4 not met: Subject Body weight is not ≥ 50 kg and ≤ 90 kg at screening	
EXCL01	Excl crt.1 met: Use of other investigational drugs within 5 half-lives of the drug or until the expected pharmacodynamic effect of the drug has returned to baseline	
EXCL02	Excl crt.2 met: Previous exposure to denosumab (Prolia, Xgeva, or biosimilar denosumab)	
EXCL20	Excl crt.20 met: Renal impairment manifesting with an estimated glomerular filtration rate (eGFR) < 45 ml/min	
EXCL23	Excl crt.23 met: Positive serology indicating Hepatitis B or Hepatitis C infections	
EXCL24	Excl crt.24 met: Positive serology for human immunodeficiency virus (HIV) infection or known diagnosis of AIDS	
WITH01	Subject not withdrawn from study after informed consent was withdrawn	If withdrawn prior to Visit 11
TRT01	Subject is dosed with expired IP	If Visit 2
TRT02	Subject is dosed with damaged IP	If Visit 2
TRT06	Any deviation from dose or regimen of IP leading to risks for subjects' safety or data integrity	If Visit 2
TRT07	Subject is dosed with IP rejected for use following temperature deviation	If Visit 2

The PKS will be the analysis set used for the PK analyses (see Sections 4.6.2.3, 4.7.3, 4.8.1 and 4.8.2). The reasons for exclusion from PKS, including exclusion flags as defined in Section 4.8.2, will be summarized by number and percentages for each treatment group. Patients will be analyzed according to the study treatment received.

2.6.7 Treatment Period 2 Randomized Analysis Set

The Treatment Period 2 Randomized Analysis Set (TP2 RAS) is a subset of TP1 RAS and consists of all patients who were re-randomized into TP2. The TP2 RAS will include any patients who were re-randomized into TP2 including those that were not treated in TP2.

A patient will be included in TP2 RAS, if the patient was included in TP1 RAS and a valid randomization date for TP2 is available.

The TP2 RAS will be used for the description of study disposition in TP2 (see Section 4.2).

2.6.8 Treatment Period 2 Full Analysis Set

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

Specifically this means at least one of the following conditions must be met:

- For efficacy this means that there is a DXA scan measurement available after first TP2 dose (for any of LS-BMD, TH-BMD or FN-BMD).
- For PD either one CTX sample concentration or one PINP sample concentration value is available after first TP2 dose.
- For the PK there is one denosumab concentration available after first TP2 dose.

The TP2 FAS will be the analysis set used for PK, PD and efficacy secondary endpoints in TP2 (see Sections 4.6.2.2 to 4.6.2.3, 4.7.1 to 4.7.3, 4.8.1 and 4.8.3).

2.6.9 Treatment Period 2 Safety Analysis Set

The Treatment Period 2 SAF (TP2 SAF) includes all patients who received at least one dose of study medication in TP2. Patients will be analyzed according to the treatment received in TP2.

A patient will be included in TP2 SAF if the patient was included in TP2 RAS and at least one non-missing non-zero dose of study drug of either GP2411 or Prolia was collected in TP2.

The TP2 SAF will be the analysis set used for the safety endpoints in TP2 (see Sections 4.4 and 4.7.4).

3 Changes to planned analyses

Fractures are specified in more detail to focus comparison on those fractures due to osteoporosis (see Section 4.7.4.3).

The margin for the primary endpoint analysis of %CfB in LS-BMD at Week 52 for EMA requirement was updated from 2.00% to 1.45% following EMA feedback in the follow up scientific advice from 27-Jan-2022 to retain at least 70% of the minimum treatment effect (see Section 2.4.2).

4 Statistical analyses

4.1 General considerations

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, SD, minimum, median and maximum value. For continuous PK and PD parameters (except the time to reach maximum concentration (Tmax), where only median, minimum and maximum values will be presented) as well as serum drug, CTX and PINP concentrations, the CV% (i.e. SD divided by arithmetic mean), geometric mean and geometric coefficient of variation (%) (geometric CV%, except for %CfB in CTX or PINP which may be negative and therefore no geometric mean or geometric CV% can be calculated) will also be presented.

Only scheduled PK and PD samples will be included in PK and PD parameter derivation and descriptive statistical analysis.

Geometric CV% will be calculated using the following formula:

$$geometric\ CV\% = 100 \times \sqrt{exp(SD^2) - 1} \quad \text{(E1)}$$

where SD is the SD of the natural-logarithmically-transformed data.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of patients included in the analysis set under consideration unless otherwise specified.

The following conventions are applied for reporting descriptive statistics of all continuous endpoints with the exception of PK and PD endpoints. For presentation the mean and median will be presented to 1 decimal greater than the original data, SD will be 2 decimal places greater than the original data and the minimum and maximum will have the same number of decimal places as the original data.

For PK and PD endpoints CV% and geometric CV% will be presented with 1 decimal place and all other values with 3 significant digits.

Summary statistics will be presented by treatment group (and day and time point, if applicable) unless otherwise stated.

For TP1 the following treatments group will be presented:

- GP2411
- Prolia
- Total (for patient disposition, demographics and baseline characteristics only)

For TP2 the following treatment groups will be presented:

- GP2411/GP2411
- Prolia/Prolia
- Prolia/GP2411
- Total (for patient disposition, demographics and baseline characteristics only)

Target visit days as defined in the CSP will be used to calculate and present summary statistics.

Unless otherwise stated, summary tables will be on all patients included in the analysis set under consideration.

Baseline for post-dose evaluations is defined as the last observation recorded before the first study drug administration in each treatment period.

Change from baseline will be calculated as:

$$Change\ from\ baseline = postdose\ value - baseline\ value$$

Percentage change from baseline (%CfB) will be calculated as:

$$Change\ from\ baseline\ (\%) = 100 * \frac{postdose\ value - baseline\ value}{baseline\ value}$$

With the exception of unscheduled measurement used as baseline, unscheduled measurements will be excluded from the descriptive statistical analysis. The same rule applies to PK and PD visits.

All safety data will be analyzed to the extent available and no imputations for missing safety data will be performed unless otherwise stated.

4.2 Disposition of patients and protocol deviations

4.2.1 Informed consent, screen failures and randomization

The number of patients screened, re-screened, randomized, re-randomized and not randomized will be given. In addition, the reasons for patients not being randomized will be presented.

The number of patients screened, randomized and discontinued will be presented by country and site.

Randomization allocation including stratification information will be listed.

4.2.2 Patient disposition

Patient disposition for each treatment period will be summarized (n and percentages). Percentages will be based on the number of patients in TP1 RAS for the TP1 disposition tables and on the number of patients in TP2 RAS for the TP2 disposition tables.

TP1 (Day 1 to Week 52)

The following information will be presented

- Number of patients treated
- Number of patients who completed TP1
  - Number of patients who discontinued treatment but continued study in TP1
    - Reason for discontinuation from treatment in TP1
- Number of patients who terminated the study prematurely in TP1
  - Reason for discontinuation from study in TP1
- Number of patients included in TP1 RAS
- Number of patients included in TP1 SAF

- Number of patients included in TP1 FAS
- Number of patients included in the PPS
- Number of patients included in the PKS
- Number of patients included in the PDS

TP2 (Week 52 to Week 78)

The tabulations will include the following information:

- Number of patients treated in TP2
- Number of patients ongoing in TP2 (interim analysis only)
- Number of patients who completed TP2
    - Number of patients who terminated the study prematurely in TP2
        - Reason for discontinuation from study in TP2
- Number of patients included in the TP2 RAS
- Number of patients included in the TP2 SAF
- Number of patients included in the TP2 FAS

Patient status will be listed by period and on overall study level. Allocation of patients to analysis sets will be listed.

4.2.3 Protocol deviations

All protocol deviations will be reviewed on an ongoing basis prior to partial database lock for the interim analysis. The protocol deviations leading to exclusion from PPS, PDS or PKS analysis sets are shown Table 2-9, Table 2-10 and Table 2-11. The protocol deviations in this SAP are based on version 14.0 of the protocol deviation specifications. This classification concerns the impact that the protocol deviations are expected to have on the statistical analysis.

The protocol deviations leading to exclusion of patients from any of the analysis sets will be summarized for all patients in TP1 RAS.

A summary will be provided for all important protocol deviations occurring during TP1 (including Screening) for the TP1 RAS and in TP2 for the TP2 RAS. These summary tables will be repeated subset to all protocol deviations related to COVID-19 for any reason.

Protocol deviations will be listed with specific relationship to COVID-19 included.

4.3 Demographics and baseline characteristics

All summaries of demographic and baseline characteristics will be provided in TP1 for the TP1 SAF, TP1 FAS, PPS, PKS and PDS analysis set and in TP2 for the TP2 FAS and TP2 SAF. Demographic and baseline characteristics will be repeated for TP1 FAS on the subgroup of Japanese patients (region=Japan and race=Japanese) and on the subgroup of patients enrolled pre-COVID and during-COVID. The COVID period ‘start’ date of potential impact of the COVID-19 epidemic on the estimation of treatment effect in our clinical trials, in a given country or region, is being defined as the approximate time point at which, according to the WHO situation reports and the Johns Hopkins database, the number of confirmed COVID-19 infections started to increase significantly (around 100 confirmed cases) and / or governments

started to take measures (such as lockdown and stay-at-home orders) to contain the spread of the infection, whichever occurred first. This is defined as 21-Feb-2020 for Japan and 01-Mar-2020 for US and Rest of the World.

Continuous demographic parameters (age, height and weight) will be summarized by means of descriptive statistics by treatment group. Age group (<65 years/ >=65 years), weight group (<70 kg/ ≥70 kg), region (US, Rest of World, Japan), race and ethnicity will be summarized by number and percentages for each treatment group.

Baseline characteristics, including LS-BMD, FS-BMD, TH-BMD, CTX and PINP and prior bisphosphonate use (yes/no, ATC code: M05BA and M05BB) will be summarized for each treatment group and will be repeated for TP1 FAS on the subgroup of patients enrolled pre-COVID and during-COVID.

Medical history will be summarized (number and percentage of patients) by system organ class (SOC) and preferred term (PT) in TP1 for TP1 SAF and in TP2 for TP2 SAF.

4.4 Treatment regimen, compliance and exposure to drug

The number and percentage of patients and patient time (months) will be summarized by treatment (not treatment arm) and number of doses received. The percentage of patients will be based on the number of patients in the TP1 SAF.

Patient time will be calculated as

$$Patient\ time\ (months) = \frac{Date\ of\ last\ visit - Date\ of\ first\ dose + 1}{30.25}$$

A listing will be provided showing the drug product batches used by patient.

4.5 Concomitant medications

Prior medications are defined as medications stopping before first dose. Concomitant medications are such that are given concomitantly with the study drug. Medications where it is unclear which study period they apply to (e.g. no time of administration or indication why the medication was given) will be allocated to both treatment periods.

Prior osteoporosis medications will be summarized (number and percentage of patients) by anatomical therapeutic chemical (ATC) class (level 2) and preferred term.

Concomitant medications will be summarized (number and percentage of patients) by ATC class (level 2) and preferred term. Significant non-drug therapies will be summarized (number and percentage of patients) by SOC and preferred term. Summary tables will be provided for each treatment period (TP1, TP2) separately: in TP1 for TP1 SAF and in TP2 for TP2 SAF.

Vitamin D and calcium medications (prior or concomitant) will be listed for all patients in TP1 SAF. Vitamin D and calcium medications are defined by using ATC codes, A11CC and A11CB and A12A.

4.6 Analysis of the primary endpoints

The main objective of this study is to demonstrate similar efficacy, PD and PK of GP2411 and Prolia (EU-authorized) in postmenopausal women with osteoporosis. This will be done by comparing %CfB of LS-BMD (IQC and X-cal corrected) at Week 52 as well as AUEC of %CfB in serum CTX and AUCinf and Cmax after the first dose, following injection of either treatment every six months.

4.6.1 Definition of primary endpoint(s)

A list of primary endpoints with respective primary analysis sets applicable to different health authorities is provided in Table 2-3.

Definitions of AUEC, Cmax and AUCinf and can be found in Section 4.8.

4.6.2 Statistical model, hypothesis, and method of analysis

The type I error rate will be controlled on health authority requirement level, i.e. a separate hierarchical testing strategy will be implemented per health authority. Testing strategy for FDA can be found in Table 4-1, testing strategy for EMA in Table 4-2 and testing strategy for PMDA in Table 4-3:

Table 4-1 Hierarchical testing strategy for FDA

Endpoint		Equivalence criteria	Analysis set
Step 1	%CfB in LS-BMD at Week 52	95% CI for difference in means contained in [-1.45%, 1.45%]	TP1 FAS
Step 2	AUEC of %CfB in serum CTX after first dose*	90% CI for ratio of geometric means contained in [0.80, 1.25]	PDS

* Secondary endpoint

Table 4-2 Hierarchical testing strategy for EMA

Endpoint		Equivalence criteria	Analysis set
Step 1	%CfB in LS-BMD at Week 52	95% CI for difference in means contained in [-1.45%, 1.45%]	PPS
Step 2	AUEC of %CfB in serum CTX after first dose	95% CI for ratio of geometric means contained in [0.80, 1.25]	PDS

Table 4-3 Hierarchical testing strategy for PMDA

Endpoint		Equivalence criteria	Analysis set
Step 1	%CfB in LS-BMD at Week 52	95% CI for difference in means contained in [-2.00%, 2.00%]	TP1 FAS
Step 2	Serum PK parameter AUCinf after first dose	90% CI for ratio of geometric means contained in [0.80, 1.25]	PKS
	Serum PK parameter Cmax after first dose	90% CI for ratio of geometric means contained in [0.80, 1.25]	PKS
Step 3	AUEC of %CfB in serum CTX after first dose*	95% CI for ratio of geometric means contained in [0.80, 1.25]	PDS

* Secondary endpoint

For all testing strategies, each subsequent step will only be performed if the previous step was successful.

4.6.2.1 Efficacy endpoint

4.6.2.1.1 Primary analysis

For EMA the primary analysis will be performed on the PPS which is considered the most sensitive analysis set to use when testing for equivalence. For FDA and PMDA the primary analysis will be performed on the TP1 FAS to reduce potential selectivity bias undermining the integrity of the randomization by including all available data (see Table 2-3). The respective other analysis set will be used as supplementary analysis (see Section 4.6.2.1.3).

IQC and X-cal corrected BMD will be used for primary analysis and vertebrae exclusions will be applied up to Week 52 (more detailed information how the corrections are applied can be found in Imaging Project Plan v5). Analyses for TP1+TP2 of IQC and X-cal corrected BMD will be based on vertebrae exclusions up to Week 78.

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

$H_0: |GP2411 - Prolia| \geq \Delta$

versus

$H_1: |GP2411 - Prolia| < \Delta$

Therapeutic equivalence in terms of %CfB in LS-BMD will be concluded following PMDA requirement if the two-sided 95% CI for the difference in mean changes is contained within the interval [−2.00%, 2.00%], and for FDA and EMA requirement if the 95% CI of the difference is contained within the interval [-1.45%, 1.45%] (see Table 2-3).

A mixed-model repeated measures (MMRM) analysis will be performed for %CfB as the endpoint including the following categorical variables:

- treatment (GP2411, Prolia)
- Prior bisphosphonate use (yes/ no) as categorical variable
- DXA machine type (Lunar, Hologic)
- time (visits Week 26, Week 52) as a categorical variable
- the interaction between time (visits Week 26, Week 52) and treatment (GP2411, Prolia)
- baseline LS-BMD values as a continuous covariate

The primary analysis will be based on the least-squares mean treatment differences at the Week 52 time point (and not on the overall treatment differences). Mean change from baseline at Week 52, standard errors and the two-sided 95% CIs for the mean difference between GP2411 and Prolia at Week 52 will be estimated from the model and the respective CI compared to the pre-specified equivalence range of [-Δ; Δ].

If the baseline LS-BMD is missing then no %CfB can be calculated for any post-baseline visit, and the patient will not be included in the primary analysis. If the Week 26 LS-BMD is missing then the value of %CfB is missing at Week 26, but the missing value will be assumed missing

at random (using the MMRM model) and the patient could still be included in the above specified MMRM if the Week 52 %CfB is available. If the Week 52 is missing then the %CfB at Week 52 cannot be calculated, and the patient will not be included in the primary analysis using the PPS but will be included in the primary analysis using the TP1 FAS.

The SAS code to perform the analysis is given below in Table 4-4.

Table 4-4 SAS code for the primary efficacy analysis of LS-BMD

```
PROC MIXED DATA=adeff ORDER=INTERNAL PLOTS=VCIRYPANEL;
  CLASS usubjid  treatment DXA_type visit prior_bisphos;
  MODEL pchg = treatment DXA_type visit treatment*visit baseline prior_bisphos / DDFM
= KR RESIDUAL OUTPM=residual VCIRY;
  REPEATED visit /  SUB = usubjid TYPE = UN;
  LSMEANS treatment*visit;
  ESTIMATE "LS-BMD : GP2411 versus Prolia" treatment 1 -1 treatment*visit 0 1 0 -1 /
CL ALPHA=0.05;
RUN;
```

Note: alpha = 0.05 defines the two-sided significance level, i.e. a 95% CI will be calculated

Stratification factor region (US, Rest of World, Japan) is considered an administrative stratification factor and therefore not included in the statistical model.

Stratification factor age (<65 years/ ≥65 years) can best be assumed to have a linear effect on LS-BMD (van Schaik et al 2015) and therefore using the %CfB in LS-BMD as primary endpoint and including LS-BMD Baseline value as covariate should already account for the change in LS-BMD with age.

Stratification factor prior bisphosphonate use (yes/ no) was identified as a potential source of heterogeneity for the primary endpoint of LS-BMD that cannot be assured to be completely controlled though the use of inclusion/exclusion criteria and is therefore included in the model.

Stratification factor body weight group (<70 kg/ ≥70 kg) is not expected to have a relevant impact on LS-BMD and is therefore not included in the model for LS-BMD. This stratification factor was set up to ensure interpretable PK analyses.

For DXA machine type there is a concern, although the %CfB is used and should adjust for different DXA machine types, that if this adjustment is insufficient and that it would be prudent to include an adjustment for DXA machine type.

The model includes data for each patient from both the Week 26 and Week 52 BMD measurements. This is done to increase the statistical power of the model as Week 26 LS-BMD values will be correlated with Week 52 values. This is differentiated in the model by the use of the time factor. However, it is highly likely that the treatment difference at Week 26 and Week 52 are not identical and hence a treatment by visit interaction is included.

The most flexible covariance matrix being unstructured will be assumed, that is, all variance and covariance parameters are estimated from the data. This will allow adjustment for

correlation in LS-BMD values across visits within patients. If the unstructured covariance matrix results in a lack of model convergence, an appropriate covariance structure will be selected and specified in the SAP before interim database lock.

The denominator degrees of freedom will be calculated using the Kenward-Roger method.

Results of the primary efficacy analysis will be presented showing number of patients for each treatment, adjusted (LS mean) changes with standard error (SE), LS mean treatment difference with SE and 95% CI. In addition, the 95% confidence interval with a margin of (-1.45%, 1.45%) using the TP1 FAS and PPS and a margin of (-2.00%, 2.00%) using TP1 FAS will be presented in forest plots.

4.6.2.1.2 Sensitivity analysis

Sensitivity analysis to assess robustness of normality assumption of MMRM

In case the %CfB LS-BMD the residuals of the MMRM for the %CfB LS-BMD analysis are not approximately normally distributed (i.e. as assessed using a Q-Q plot) then a 95% non-parametric Hodges-Lehmann CI for the difference between the treatment groups at Week 52 on the subset of patients with a Week 52 %CfB in LS-BMD value available will also be calculated. This will be done in order to assess the sensitivity of the results to a possible departure from the normality assumption underlying the MMRM. Q-Q plot will be performed on scaled marginal residuals using PROC UNIVARIATE with NORMAL option and provided as part of the Appendix 16.1.9. The SAS code to perform the sensitivity analysis is given below in Table 4-5.

Table 4-5 SAS code for the Hodges-Lehmann analysis of LS-BMD

```
PROC NPAR1WAY DATA=adeff  HL (REFCLASS=2) ALPHA = 0.05;
  CLASS treatment;
  VAR pchg;
  ODS SELECT HodgesLehmann;
RUN;
```

Note: alpha = 0.05 defines the two-sided significance level, i.e. a 95% CI will be calculated

Sensitivity analysis to assess robustness of MAR assumption for MMRM

The primary analysis of %CfB in LS-BMD on the TP1 FAS will assume missing data is MAR and this data will be taken care of by the MMRM model (see Section 4.6.2.1.1).

A sensitivity analysis in form of a tipping point analysis will be carried out using multiple imputation (MI) methods to impute missing %CfB in LS-BMD at Week 52 values not directly related to the COVID-19 pandemic by making estimated values worse up to a δ of -2%. Values related to COVID-19 pandemic are considered to be missing at random and therefore do not get imputed MNAR. This analysis is to explore the potential impact of different assumptions about the missing data patterns.

Values are considered related to COVID-19 pandemic if at least one of the following is true

- Week 52 LS-BMD value is missing with COVID-19 related protocol deviation OTH01, OTH9A, or OTH31 recorded in Week 52.
- Patient discontinued study between week 26 and week 52 with COVID-19 related protocol deviation OTH32 recorded.

The following MI algorithm for missing (in the article referred to as postdeviation) data will be used as proposed by Carpenter et al 2013:

1. For each treatment arm, take all patient's predeviation (non-missing) data and – assuming MAR – fit a multivariate normal distribution with unstructured mean and unstructured variance-covariance matrix.
2. Separately for each treatment arm, draw a mean vector and variance-covariance matrix from the posterior distribution
3. For each patient who has no Week 52 value, use the draws from step 2 to build the joint distribution of that patient's pre- (Week 26) and postdeviation (Week 52) outcome data
4. For each patient who has no Week 52 value, construct the conditional distribution of postdeviation (Week 52) data given predeviation (Week 26) outcome data. Sample the postdeviation data from this conditional distribution, to create a completed data set
5. Repeat steps 2 to 4 25 times, resulting in 25 imputed data sets
6. Fit the MMRM model to each imputed data set, and combine the resulting parameter estimates and standard errors using Rubin's rules (see Rubin 1987) for final inference

To build the joint distribution of pre- (Week 26) and postdeviation (Week 52) outcome data (Step 3), a proposal by Koch 2008 adapted to the biosimilar setting will be followed. For a non-inferiority trial Koch proposes to replace missing data for all patients in both the reference (in our case the originator, Prolia) and the experimental groups (in our case the biosimilar, GP2411) according to an arguably reasonable method as a first step. As a second step all imputed values for the experimental group are made worse by the non-inferiority margin δ. Adapting the proposal by Koch to a biosimilar setting, adaptions will be made separately to both the biosimilar and reference arms. Hereby, the joint distribution of pre- (Week 26) and postdeviation (Week 52) for the treatment arm on which adaptions are performed will be created as bivariate normal distribution with mean $\mu_i = \begin{pmatrix} \mu_{Week\ 26} \\ \mu_{Week\ 52} - \delta \end{pmatrix}$ and the variance-covariance matrix estimated in step 2 of Carpenter's algorithm.

To increase the information gained from Koch's proposal, the analysis will be performed using δ ranging from -2.00% to 0% using 0.05% steps. This will thereby provide a tipping point analysis showing not only study conclusion robustness assuming missing data are worse by the clinically relevant margin, but potentially also the maximum difference in treatment effect for missing data that would not change study conclusions.

As specified in Carpenter et al 2013, analyses using SAS PROC MI with a Markov chain Monte Carlo method and BY "treatment arm" options and Carpenter's group macro for randomized-arm MAR option are computationally equivalent, and the results are the same up to Monte Carlo variation. As in our case data have a monotone missing pattern, a regression method will be used instead of Markov chain Monte Carlo.

Thus, tipping point analysis will be implemented in SAS in 3 steps:

1. All missing Week 26 values are imputed using PROC MI MCMC method with 25 imputations to achieve monotone missing data pattern, then for every imputation all missing Week 52 values are imputed using PROC MI regression method with one imputation, imputed Week 52 values not directly related to the COVID-19 pandemic are also adjusted separately in biosimilar and reference arms by δ ranging from -2.00% to 0% using 0.05% steps (see SAS code in Appendix 2)
2. Original MMRM model is fitted to each imputed data set and each δ for biosimilar and reference arms (using code provided in Table 4-4 with BY statement for adjusted arm, delta and imputation number)
3. Resulting parameter estimates and standard errors are combined using PROC MIANALYSE (see Table 4-6)

Table 4-6 SAS code for combining results from multiple imputation analysis

```
PROC MIANALYZE DATA=EstimatesMI;
  BY Adjusted_arm Delta;
  MODELEFFECTS Estimate;
  STDERR StdErr;
  ODS OUTPUT ParameterEstimates=Result;
RUN;
```

Sensitivity analysis to assess impact of randomization errors

Equivalence analysis based on the TP1 FAS will be repeated as sensitivity analysis assigning patients to treatment actually received and the stratification factors as derived from values stored in the clinical database. Equivalence analysis based on the PPS will be repeated as sensitivity analysis assigning patients to stratification factors as collected in the IRT.

Sensitivity to assess impact of forced randomizations

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

4.6.2.1.3 Supplementary analysis

Descriptive statistics of LS-BMD and %CfB in LS-BMD are described in Section 4.7.1.

For LS-BMD primary analysis from both PPS and TP1 FAS, the analysis set that is not considered primary will be used as supportive analysis using the methodology as specified for the primary analysis for the respective other analysis set in Section 4.6.2.1.1.

4.6.2.1.4 Subgroup analyses

Equivalence analysis based on the TP1 FAS will also be repeated on the subgroup of Japanese patients (region=Japan and race=Japanese). The 80% confidence interval with a margin of (-2.00%, 2.00%) will be presented but without inference on equivalence as compared to the margin given the small sample size of this subgroup.

4.6.2.2 PD endpoint

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

The assessment of PD similarity will be based upon the 95% CIs of the ratio of the geometric means (GP2411/Prolia) for the AUEC of %CfB in serum CTX concentrations after first dose, which have to be contained entirely within the pre-specified acceptance interval of [0.8000, 1.2500], i.e. when rounded to 4 decimal places. Unless relevant, however, estimate and confidence interval will be presented with 2 decimal places only.

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

$$H_0: \mu_{PK,T}/\mu_{PK,R} \leq 0.8000 \; or: \; \mu_{PK,T}/\mu_{PK,R} \geq 1.2500$$

versus

$$H_1: 0.8000 < \mu_{PK,T}/\mu_{PK,R} < 1.2500$$

Analyses of covariance (ANCOVA) will be performed on the log-transformed AUEC. The ANCOVA model will include the following variables

- treatment as a fixed factor
- log(baseline CTX) value as a continuous covariate

The ANCOVA will include calculation of least-squares means (LSM) for the treatments. The ratios of LSM will be calculated using the exponentiation of the LSM from the analyses on the corresponding log-transformed AUEC. Consistent with the two one-sided tests for biosimilarity at the 2.5% significance level (Schuirmann 1987), 95% CI for the ratio will be derived for AUEC. The denominator degrees of freedom will be calculated using the Kenward-Roger method.

The SAS code to perform the analysis is given below in Table 4-7.

Table 4-7 SAS code for the primary analysis of CTX AUEC

```
PROC MIXED DATA=adpd ORDER=INTERNAL;
  CLASS treatment;
  MODEL logAVAL = treatment log(baseline) / DDFM=KR;
  LSMEANS treatment;
  ESTIMATE "CTX: GP2411 versus Prolia" treatment 1 -1 / CL ALPHA=0.05;
RUN;
```

Note: alpha = 0.05 defines the two-sided significance level, i.e. a 95% CI will be calculated. Alpha = 0.1 for analysis with 90% CI to be used

Stratification factors age, prior bisphosphonate use, weight and region were implemented for other reasons than impact on AUEC of %CfB in CTX (see Section 4.6.2.1) and therefore are not included in the model.

Results of the primary PD analysis will be presented descriptively showing number of patients for each treatment, adjusted LS geometric means, geometric mean ratio with SE and 95% CI.

The analysis will be repeated using 90% CI as secondary endpoint for FDA.

In addition, the 95% and 90% confidence intervals with margin (0.80,1.25) using PDS will be presented in forest plots on a logarithmic scale.

Descriptive statistics of AUEC of %CfB in serum CTX concentrations after the first dose will be presented by TP1 treatment group and will include the number of values >0.

Descriptive statistics of AUEC of %CfB in serum CTX concentrations after the first dose by TP1 treatment group will be repeated for Japanese patients (region=Japan and race=Japanese) only as a subgroup analysis.

4.6.2.3 PK endpoints

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

The assessment of PK similarity will be based upon the 90% CIs for the ratio of the geometric means (test/reference) for the AUCinf and Cmax which have to be contained entirely within the pre-specified PK acceptance interval of [0.8000, 1.2500], i.e. when rounded to 4 decimal places. Unless relevant, however, estimates and confidence intervals will be presented with 2 decimal places only.

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

$H_0: \mu_{PK,T}/\mu_{PK,R} \leq 0.8000 \; or: \; \mu_{PK,T}/\mu_{PK,R} \geq 1.2500$

versus

$H_1: 0.8000 < \mu_{PK,T}/\mu_{PK,R} < 1.2500$

ANCOVA will be performed on the log-transformed PK parameters. The ANCOVA model will include the following variables

- treatment as a fixed factor
- weight as a continuous covariate

The ANCOVA will include calculation of LSM for the treatments. The ratios of LSM will be calculated using the exponentiation of the LSM from the analyses on the corresponding log-transformed PK parameter. Consistent with the two one-sided tests for bioequivalence at the 5% significance level (Schuirmann 1987), 90% CIs for the ratio will be derived for respective PK parameter. The denominator degrees of freedom will be calculated using the Kenward-Roger method.

The SAS code to perform the analysis is given below in Table 4-8.

Table 4-8 SAS code for the primary analysis of PK parameters

```
PROC MIXED DATA=adpp ORDER=INTERNAL;
  BY paramcd;
  CLASS treatment;
  MODEL logAVAL = treatment weight / DDFM=KR;
  LSMEANS treatment;
  ESTIMATE "PK: GP2411 versus EU-Prolia" treatment 1 -1 / CL ALPHA=0.10;
RUN;
QUIT;
```

Note: alpha=0.10 defines the two-sided significance level, i.e. a 90% CI will be calculated

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

Results of the primary PK analysis will be presented descriptively showing number of patients for each treatment, adjusted LS geometric means, geometric mean ratio with SE and 90% CI. In addition, the 90% confidence interval with margin (0.80, 1.25) using PKS will be presented in a forest plot on a logarithmic scale.

Descriptive statistics of AUCinf and Cmax will be presented by TP1 treatment group and in addition by TP1 treatment group and weight group (<70 kg/ ≥70 kg).

Descriptive statistics of AUCinf and Cmax by TP1 treatment group will be repeated for Japanese patients (region=Japan and race=Japanese) only as a subgroup analysis.

4.7 Analysis of secondary endpoints

4.7.1 Efficacy endpoints

Analysis of the primary efficacy endpoint %CfB in LS-BMD at Week 52 is described in Section 4.6.2.1.

LS-BMD is defined as a BMD measurement from DXA scan with location=lumbar spine, FN-BMD – with location=femoral neck, TH-BMD – with location=femur. If not specified otherwise, IQC + X-cal corrected BMD shall be used for analysis.

TP1 (Day 1 to Week 52)

The following analyses will be provided for other efficacy endpoints for TP1 FAS and PPS unless otherwise stated:

- LS-BMD, FN-BMD, TH-BMD values and associated %CfB will be summarized descriptively by TP1 treatment group for baseline, Week 26 and Week 52
- LS-BMD values and associated %CfB will be summarized descriptively by TP1 treatment group for baseline, Week 26 and Week 52 for all Japanese patients (region=Japan and race=Japanese) only as a subgroup analysis for TP1 FAS

TP1 + TP2 (Day 1 to Week 78)

The following analyses will be provided for other efficacy endpoints for TP2 FAS:

- LS-BMD, FN-BMD, TH-BMD values and associated %CfB will be summarized descriptively by TP2 treatment group for baseline, Week 26, Week 52 and Week 78
- LS-BMD values and associated %CfB will be summarized descriptively by TP2 treatment group for baseline, Week 26, Week 52 and Week 78 for all patients from Japan as a subgroup analysis

BMD parameters will be listed.

4.7.2 PD endpoints

Analysis of AUEC of %CfB is described in Section 4.6.2.2.

TP1 (Day 1 to Week 52)

The following analyses will be provided for PDS:

- CTX and PINP serum concentrations values and associated %CfB will be analyzed using summary statistics by TP1 treatment group and visit
- A plot of the arithmetic mean (± SD) for %CfB in CTX and %CfB in PINP serum concentrations will be produced by TP1 treatment group and visit
- Summary statistics of the rebound area will be presented by TP1 treatment group to demonstrate robustness of the co-primary CTX AUEC endpoint

TP1 + TP2 (Day 1 to Week 78)

The following analyses will be provided for TP2 FAS:

- CTX and PINP serum concentrations values and associated %CfB will be analyzed using summary statistics by TP2 treatment group and visit between baseline and completion of Week 78

Analyses on the primary endpoint of CTX AUEC are described in Section 4.6.2.2. Handling of CTX/PINP serum concentrations below LLOQ and handling of SD whiskers in graphs for %CfB in CTX/PINP serum concentrations where mean-SD <-100% are described in Section 4.8.4.

PD parameters as well as CTX and PINP serum concentrations will be listed.

4.7.3 PK endpoints

Analysis of PK parameters AUCinf and Cmax is described in Section 4.6.2.3.

TP1 (Day 1 to Week 52)

The following analyses will be provided for PKS:

- Denosumab serum concentrations values will be summarized descriptively by TP1 treatment group and visit
- Arithmetic mean (± SD) denosumab serum concentration time profiles after the first dose in TP1 will be presented in both linear as well as semi-logarithmic scale

TP1 + TP2 (Day 1 to Week 78)

The following analyses will be provided for TP2 FAS:

- Denosumab serum concentrations values will be presented using summary statistics by TP2 treatment group and visit between baseline and completion of Week 78

Summary of further PK parameters is described in Section 4.8.2.

PK parameters including denosumab serum concentrations will be listed. Tmax will be presented with 2 decimals and AUC%extrap with 1 decimal, all other parameters with 3 significant digits.

For concentration time profiles lower SD whisker will not be presented if mean-SD <0. On semi-log scale values of 0, for which no log transformation is defined, will be presented as 1.

4.7.4 Safety endpoints

Safety analyses will be presented for TP1 for the TP1 SAF, and for TP1 + TP2 (Day 1 to Week 78) for the TP2 SAF. In addition, Analyses of endpoints not presented by visit will be presented for TP2 (Week 52 to Week 78) for the TP2 SAF in addition.

4.7.4.1 Adverse events

An AE is the appearance or worsening of any undesirable sign, symptom, or medical condition.

General considerations for AEs

Treatment-emergent AEs (TEAEs) are defined as AEs that started after the first dose of study medication or events present prior to the first dose of study medication but increased in

severity). If it is unclear from the onset date if the onset was prior to dosing at Day 1 then the AE will be considered treatment emergent.

TEAEs with an onset date (and time) from Day 1 up until dosing on Visit 15 will be assigned to TP1. TEAEs with an onset date (and time) after dosing at Visit 15 will be assigned to TP2. In cases where it is unclear from the onset date (and time) if the onset was prior to dosing at Visit 15 then the TEAE will be assigned to both TP1 and TP2 but will only be counted once in the TP1 + TP2 analysis.

Summary of AEs

The number (and percentage) of patients with TEAEs based on preferred term will be summarized in the following ways:

- by treatment group, primary system organ class and preferred term.
- by treatment group, primary system organ class, preferred term and maximum severity

Separate summaries will be provided for study treatment related adverse events, serious adverse events, and adverse events leading to study discontinuation

A patient with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

In addition, an overview of TEAEs will be presented (including number and percentage of patients). The overview will show any AE regardless of relationship to study drug as well as treatment-related AEs and AEs with any grade as well as grade 3/4 for the following types of AEs:

- All AEs
- SAEs
- Fatal SAEs
- AEs leading to study drug discontinuation
- AEs leading to study discontinuation

Listing of death, serious adverse events, adverse events leading to study drug or study discontinuation will be provided. A separate listing will be provided for all AEs.

For ease of reporting, the summary table showing number (and percentage) of patients with TEAEs by treatment group, primary system organ class and preferred term for TP1 using TP1 SAF and for TP2 using TP2 SAF will be repeated showing only TEAEs with an incidence greater than or equal to 3% in any treatment group.

Disclosure requirements for AEs

For the legal requirements of EudraCT, two required tables on treatment emergent adverse events will be provided by system organ class and preferred term:

- not serious adverse events with an incidence greater than 3% in any treatment group
- SAEs and SAE suspected to be related to study treatment

Summaries will be provided separately for TP1 using TP1 SAF and TP2 using TP2 SAF, but within one table shell resulting in the following 5 treatment arms within each summary table:

- GP2411 TP1, TP1 SAF
- Prolia TP1, TP1 SAF
- GP2411/GP2411 TP2, TP2 SAF
- Prolia/Prolia TP2, TP2 SAF
- Prolia/GP2411 TP2, TP2 SAF

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is >1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE/ SAE suspected to be related to study treatment/ non SAE has to be checked in a block e.g., among AE's in a ≤1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

4.7.4.2 Injection site reactions

Treatment-emergent injection site reactions (ISR) will be summarized (including number and percentage of patients). The ISR overview will show any for the following categories:

- Any ISRs
- ISRs by Grade (Grade 1 to Grade 4)
- Serious ISRs
- ISRs leading to discontinuation

4.7.4.3 Fractures

There are two type of fractures that will be collected throughout the study

- New and worsening vertebral fractures
- New nonvertebral (including hip) fractures

New and worsening vertebral fractures are defined as occurrence of new fracture (i.e. change in Genant score from 0 at baseline to 1 or higher at a later time point) or worsening fracture (i.e. increase in Genant score from baseline at a later time point) in any vertebra from thoracic vertebra 4 (T4) to lumbar vertebra 4 (L4). The new and worsening vertebral fractures will be identified based on central reading of lateral thoraco-lumbar spine X-ray.

New nonvertebral fracture (including hip fractures) will be recorded as adverse events and are identified by the preferred terms as listed in Appendix 4.

Number and percentage of patients with at least one adverse event reported non-vertebral (including hip fractures) will be summarized by treatment group for TP1, TP2 and TP1+TP2.

Number of subjects with at least one vertebral fracture at baseline, new vertebral fractures, and worsening vertebral fracture based on central imaging data will be summarized by treatment group for TP1, TP2 and TP1+TP2.

A listing of patients with any adverse event reported non-vertebral (including hip fractures) will be provided.

4.7.4.4 Laboratory evaluation

Blood and urine samples will be taken for laboratory safety tests as indicated in Appendix 1.

The following parameters will be measured:

Table 4-9 Laboratory assessments

Test category	Test name
Hematology	Hemoglobin, Platelets, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Albumin, Total protein, Alkaline phosphatase, ALT, AST, Lactate dehydrogenase (LDH), Calcium, Albumin adjusted serum calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Total Bilirubin, Blood Urea Nitrogen (BUN), Glucose, Serum 25 (OH) Vitamin D level
Coagulation	Prothrombin time (PT)/ International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Hepatitis serology	Hepatitis B (HBsAg, anti-HBs and anti-HBc), Hepatitis C (anti-HCV)
HIV serology	HIV-1 and HIV-2 antibodies
COVID-19 related testing	Serological test for antibodies against SARS-CoV-2

Boxplots will be provided for hematology, chemistry and coagulation parameters by visit. For ALT/AST values > 6x ULN (ULN is 41 U/L for AST, 45 U/L for ALT) and for ALP values > 5x ULN will be excluded from boxplot summary statistics for readability but will be mentioned in a footnote.

Shift table for the severity (low/high/normal with low considered worst) for Calcium will be used to compare baseline to the worst on-treatment value.

Any laboratory values given as <X.X in the database will be imputed with the value of the number without the sign for the descriptive statistics and the calculation of changes from baseline, e.g., a value of <2.2 will be imputed as 2.2 for the calculations. There will be no imputation in the data listings; all values will be displayed as recorded in the database.

For on treatment values, only scheduled lab tests will be used in tables and if there are repeated laboratory analysis of identical samples, only the first non-missing value will be used.

All abnormal hematology, chemistry and coagulation laboratory data will be listed. For patients with any abnormal values, values for all visits for that parameter will be listed separately as well.

4.7.4.5 Vital signs

For blood pressure and for some pulse rate assessments two values are measured. The average of both values will be used in any summary statistics and listings.

Vital signs including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (beats/min) and temperature and their change from baseline will be summarized by visit.

Abnormal vital signs will be listed (normal ranges for vital sign parameters are provided in Appendix 3). For patients with any abnormal values, values for all visits for the affected parameter will be listed.

4.7.4.6 12-lead ECG

Summary statistics of number of patients with clinically significant ECG abnormalities will be provided by visit.

4.7.4.7 Anti-SARS CoV2 antibody testing

Summary statistics of anti-SARS CoV2 antibody testing (e.g. positive, negative, missing) will be presented by visit and treatment group for TP1 and TP1+TP2.

4.7.5 Immunogenicity

For binding antibodies, a negative screen or negative immunodepletion means negative result; a positive immunodepletion, negative titer or any value for a titer – positive result.

For neutralizing antibodies, only one result will be reported, i.e. negative or positive.

Summary statistics of number of patients with binding and neutralizing antibodies to the study drugs will be presented by visit, treatment period and overall.

The number of transient and persistent antibodies will be summarized while persistent antibodies are those with a positive result in the binding antibody assay at their last visit.

Immunogenicity data together with Anti-SARS CoV2 status will be listed.

4.8 Pharmacokinetics and Pharmacodynamics evaluations

4.8.1 Denosumab serum concentrations

Denosumab concentrations will be listed with the scheduled (nominal) and actual sampling time point (elapsed time, up to Week 78).

If blood sampling on Visit 2, 11 or 15 is done post-dose, respective sample will be flagged and excluded from analysis.

Serum concentration data will be summarized by the scheduled visit. For handling of denosumab serum concentrations below LLOQ see Section 4.8.2.

4.8.2 PK parameters

The pharmacokinetic parameters of denosumab following the first 60 mg subcutaneous (s.c.) dose of GP2411 and Prolia will be estimated in a blinded manner by non-compartmental

analysis (best fit method) using Phoenix WinNonLin (Certara, Version 8.0 or higher) by the Clinical Research Organization (CRO) and reviewed by the Sandoz PK expert. A list of PK parameters to be calculated is presented in Table 4-10.

Table 4-10 Pharmacokinetic parameters

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

Values below LLOQ, missing data

- All concentrations below the LLOQ or missing data will be labeled as such in the concentration data listing. For summary statistics (including plots of summary statistics), all LLOQ values will be set to zero in order to calculate arithmetic means. The calculation of the geometric mean will be performed not using values below the LLOQ.
- For the calculation of PK parameters, missing denosumab serum concentrations or concentrations below LLOQ will not be imputed and handled as missing values, except for the pre-dose sample which will be treated as zero.

PK parameters

- Actual blood sampling times will be used in the PK calculations. Actual blood sampling times (elapsed time) will be calculated as the blood sampling date and time minus the date and time of the last drug administration. If the actual time is missing, the scheduled (nominal) time will be substituted to calculate the PK parameter, unless otherwise decided by the Sandoz PK expert.
- If denosumab serum concentrations are unexpectedly >LLOQ in the pre-dose sample then the following rule will be applied: if the pre-dose concentration is ≤5% of the Cmax value, the patient's data can be included without any adjustments in all PK calculations, if the pre-dose concentration is >5% of the Cmax value, the patient data will be flagged and dropped from the statistical analysis.
- PK parameters will be calculated after the first dose only. The last sample after the first dose (Visit 11) is also the pre-dose sample of the second dose, which increases the likelihood that the PK sample at Visit 11 might be collected after the second dose. In cases where the denosumab concentrations at Visit 11 are > 0.5×Cmax of a patient, then the collection of the Visit 11 sample after the second dose or a sample switch can be assumed and the Visit 11 sample will be excluded from the PK analysis.

- In calculations of AUC parameters, the linear up log down trapezoidal calculation method will be used. Extrapolation of AUClast to infinity will be done using Clast/Lambda_z, where Clast is the observed last measurable serum concentration and Lambda_z is the terminal elimination rate constant.
- Cmax and Tmax will be obtained directly from the concentration-time data. The quantification of Cmax is largely dependent on appropriate sampling schemes and missing PK samples at the expected Cmax. Due to a reduced PK sampling scheme in this study, which minimizes the burden of blood collection on patients, missing PK samples or concentrations being <LLOQ at the expected Cmax (Visit 4, Visit 5 and Visit 6) might result in unreliable Cmax, Tmax and/or AUC values. If all three PK samples at Visit 4, Visit 5 and Visit 6 are missing or the concentrations are < LLOQ, affected patients will be excluded from the PKS.
- Lamda_z will be calculated by the best fit method and calculated as the slope of the linear regression of the terminal phase of the logarithmic concentration time profile for each individual dataset available. A minimum of three data points is needed to calculate Lambda_z. The data points are chosen by examination of the semi-logarithmic concentration vs. time plot, starting with the last quantifiable concentration and moving backwards to include earlier time points, without excluding time points with quantifiable concentrations. Cmax will not be included among these data points.
- T1/2 will be determined as ln2/Lambda_z.

The statistical analyses of primary PK parameters are described in Section 4.6.2.3 and the statistical analyses of secondary PK endpoints in Section 4.7.3.

Descriptive statistics for AUClast, T1/2, AUCextrap%, Lambda_z and Tmax after first dose will be presented.

4.8.3 CTX and PINP serum concentrations

CTX and PINP serum concentrations will be given in mass per volume units and will be listed with the scheduled (nominal) and elapsed time (up to Week 78). CTX and PINP values corrected for baseline (percent change from baseline) will also be listed.

CTX exhibits a circadian rhythm which is markedly reduced by an overnight fast. It is recommended (Szulc et al 2017) that blood samples for CTX measurement should be collected in a consistent fashion following an overnight fast in the morning between 7:30 am and 10:00 am. However, as shown by Christgau et al 2000, average percentage CTX concentrations in fasted PMO women are only slightly increased at 7:00 am compared to 7:30 am and slightly decreased at 11:00 am compared to 10:00. Therefore a larger window for the CTX blood sampling (7:00 am-11:00 am) will not influence the clinical interpretation of CTX data in this study and a larger window is allowed for the CTX blood sampling (7:00 am-11:00 am). If the sampling time window (7:00 am–11:00 am) or the fasting status were violated, the respective CTX sample will be flagged and listed but excluded from the derivation of AUEC %CFB. This rule is not applicable for PINP samples.

4.8.4 PD parameters

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

The PD parameters together with the abbreviations and definitions are provided in Table 4-11.

Table 4-11 PD parameters for CTX

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

Values below LLOQ, missing data

- All CTX and PINP concentrations below the LLOQ or missing data will be labeled as such in the concentration data listing.
- For the baseline correction (percent change from baseline), calculation of PD parameters (CTX only) as well as summary statistics of CTX and PINP serum concentrations, values below LLOQ will be imputed with the actual value for the LLOQ.
- Missing CTX and PINP serum concentrations will not be imputed and handled as missing values.
- If the baseline CTX or PINP sample is missing, no baseline correction can be performed for the proceeding CTX or PINP samples. The respective sample will be flagged and the AUEC of %CfB in serum CTX cannot be calculated.
- In graphs for %CfB in CTX and PINP concentrations the lower SD whisker will not be presented if mean – SD < -100%.

PD parameters

- Actual blood sampling times will be used in the PD parameter calculations. Actual blood sampling times will be calculated as the blood sampling date and time minus the date and time of the last drug administration (elapsed time). If the actual time is missing, the scheduled (nominal) time will be substituted to calculate the PD parameter, unless otherwise decided by the Sandoz pharmacokinetics expert. PD parameters will be calculated up to Visit 11, even if Visit 11 was performed later than 26 weeks.
- For the calculations of the AUEC and the rebound area, the linear trapezoidal method will be used.
- Based on population PK/PD modeling, four CTX samples need to be at least available to estimate the AUEC of %CfB in serum CTX over 26 weeks: the baseline (pre-treatment)

CTX value, CTX values at Visit 3 or 4 to describe the decline of CTX, a CTX sample at Visit 9 or 10 and the CTX sample at Visit 11 to describe the recovery. Otherwise, the AUEC will be flagged and excluded from the analysis. An exception is made if CTX returns back to baseline before visit 11, in this case the baseline (pre-treatment) CTX value, CTX values at Visit 3 or 4, and an additional sample (Visit 7, Visit 8 or Visit 9) before CTX crosses the baseline is needed to calculate the AUEC. To calculate the rebound area values at visit 11 have to be available, otherwise the, rebound area will be excluded from the analysis. If no rebound occurs the rebound area will be 0 and included in the analysis, but only if the AUEC can be calculated.

As CTX is highly variable and can be influenced by many factors (food, circadian rhythm, sample handling and processing etc.) (Szulc et al 2017) which might affect in particular the baseline CTX values, which are used for the baseline correction, additional rules for the AUEC calculation have been pre-specified below. If any of the following rules is violated, the corresponding baseline CTX concentration will be flagged and listed. The AUEC of %CfB in serum CTX will still be calculated, but excluded from further analysis and not reported in tables or figures:

- If denosumab serum concentrations are unexpectedly >LLOQ in the pre-dose sample. Denosumab exposure at the time of baseline sampling for CTX results in an unreliable CTX baseline value and impairs the measurement of drug effect on CTX levels.
- If the pre-dose (baseline) CTX sample has been taken after dose administration, there might be an effect of denosumab on the CTX baseline value and result in an unreliable CTX baseline value that could impair the measurement of drug effect on CTX levels.

If the pre-dose (baseline) CTX sample has been taken outside the 7:00 am–11:00 am time window or the fasting status has been violated, as CTX is highly variable and can be influenced by circadian rhythm and food (Szulc et al 2017).

- If PK samples at Visit 4, Visit 5 and Visit 6 are < LLOQ, affected patients will in addition to the PKS also be excluded from the PDS, as (PK) is directly linked to PD (CTX levels) and a drug effect on CTX levels can thus not be calculated.
- If the pre-dose (baseline) CTX concentration is <1.24 fold the LLOQ (equal to 0.033×(1+0.24)=0.04092), levels. The 24% is the assay precision for the CTX LLOQ (GP2411_BA19008_BAR_PD validation_v1.0). If CTX baseline values are close to the LLOQ of the CTX assay (i.e. within the assay precision) the effect of denosumab on CTX in terms of %CfB can't be measured and will lead to unreliable %CfB values.

Statistical analyses of PD endpoints (AUEC and rebound area) are described in Sections 4.6.2.2 and 4.7.2.

4.9 Handling of missing data in the analyses

In general, with the exceptions noted below, all data will be analyzed to the extent available and no imputations for missing data will be performed.

All safety data will be analyzed to the extent available.

4.9.1 %CfB in LS-BMD

For the %CfB in LS-BMD, if the baseline LS-BMD is missing then no %CfB can be calculated for any post-baseline visit, and the patient will not be included in the primary analysis.

For the PPS and FAS primary analysis using the MMRM model as specified in Section 4.6.2.1.1 if the Week 26 or Week 52 LS-BMD is missing then the corresponding value of %CfB is missing and will not be formerly imputed, but the missing value will be assumed missing at random (MAR, using the MMRM model). Of note, patients will not be included in the primary analysis using either FAS or PPS if both the Week 26 and Week 52 LS-BMD values are missing.

With the primary efficacy analysis performed on the TP1 FAS the following missing data patterns are possible.

Table 4-12 Missing data patterns for %CfB in LS-BMD for TP1 FAS

Pattern	Baseline LS-BMD	Week 26 LS-BMD	Week 52 LS-BMD
1	Available	Available	
2	Available		Available

Pattern 1 is considered the most likely and most influential pattern in terms of missing data handling as the primary endpoint at Week 52 itself is missing. Scenario 2 is not expected to occur frequently as the LS-BMD measurement is taken at the same visit as the dosing at site is expected to be performed at site and missing a dose would lead to exclusion of patients due to safety reasons. In addition, for pattern 2 the primary endpoint at Week 52 is available and only the Week 26 value used in the model to increase comparison's power is missing.

The use of MMRM for the primary efficacy analysis is based on the assumption of MAR assuming patients with missing data behave similarly to other patients in the same treatment group with the same covariates as specified in the model, as if data was available. In general, there are two missing data mechanisms: MAR and missing not at random (MNAR). MAR assumes the probability of missing data for a patient is conditionally independent of future (current) observations, given the observed history. MNAR assumes the probability of missing data for a patient is conditionally dependent on current observations, given the observed history. Under MNAR, the future statistical behavior of patients is not the same for those who have missing data and those who do not have missing data, even if they have the same history.

The primary analysis will be based on the MAR assumption. For patients in missing data pattern 2 and patients with no missing data the primary efficacy endpoint of %CfB in LS-BMD is available. For patients with pattern 1, the development of the other patients observed in the study with non-missing Week 52 values given their own Week 26 value, is the best available estimate for the study.

To confirm robustness of conclusions using the MAR assumption, a sensitivity analysis in form of a tipping point analysis will be performed using NMAR, see Section 4.6.2.1.2.

In addition, missing data due to COVID-19 pandemic is not expected to be related to treatment effect or representative of treatment outside the context of a clinical study, further supporting the MAR assumption for missing data for the primary efficacy analysis.

Missing data patterns of %CfB in LS-BMD for TP1 FAS will be summarized by treatment group including relationship to COVID-19.

4.10 Analyses during an ongoing study

Timing and purpose of data analyses are described in Section 1 above.

The interim analysis at Week 52 will include all formal testing of the primary endpoints with full alpha level and will compare GP2411 with Prolia. The interim analysis will allow for an early read-out of primary endpoint analyses while maintaining the blind for study personnel involved in the active conduct of the study. After all patients have completed TP1, and the data for TP1 is considered clean a partial database lock will be performed for all TP1 data. The allocation of patients to analysis sets will be finalized, and the unblinding of patient treatment allocation (to both treatment periods) of study personnel involved in the reporting of results for the interim analysis but not involved the active conduct of the study will then take place.

The final analysis at Week 78 will include data collected from Week 52, after half of the patients in the Prolia arm transitioned to GP2411, until the end of the study at Week 78. The final analysis will compare the three groups “Continued GP2411” (“GP2411/GP2411”), “Continued Prolia” (“Prolia/Prolia”) and “transition into GP2411” (“Prolia/GP2411”) and will be descriptive only with no impact on primary analyses completed at Week 52. The number of patients in the three groups in Treatment Period 2 are expected to be in the approximate ratio 2:1:1 respectively. The interim analysis will include the following analyses except anti-SARS CoV2 antibody test which will be analyzed in the final analysis:

- Disposition of patients and protocol deviations for TP1 and TP2 (see Section 4.2)
- Demographics and baseline characteristics for TP1 and TP2 (see Section 4.3)
- Treatment compliance (see Section 4.4)
- Concomitant medications for TP1 and TP2 (see Section 4.5)
- Analysis of the primary endpoints (as defined in Section 4.6)
- All secondary endpoints for TP1 (see Section 4.7)
- All available safety endpoints for patients in TP2 (see Section 4.7.4).

Not all patients will have completed TP2 at the time of the interim analysis, and this analysis will be performed on available data only.

A final cumulative analysis of all data in TP1 and TP2 will be completed once all patients have completed TP2. In the final analysis, tables for TP1 only will generally not be rerun. Only tables being affected by relevant SAP updates, data changes or coding dictionary updates will be rerun, i.e.

- Adverse event tables for TP1 following coding dictionary update
- Concomitant medications for TP1 following coding dictionary update
- Medical history table following coding dictionary update
- Protocol deviation tables for TP1 following updated PD terms (with no impact on Per-Protocol set)
- Laboratory box plots for chemistry parameters following exclusion rule for extreme outliers

- Vital signs following update in duplicate measurement handling and data updates
- ECG following data updates
- Summary statistics for PD parameters following addition of number of values >0
- Summary of CTX and PINP concentrations following removal of geometric mean and CV%
- Time profiles %CfB in CTX, %CfB in PINP, drug concentrations following update of whiskers and on semi-log scale treatment of 0 value

5 References

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6 Appendices

Appendix 1: Assessment schedule

Period	Screening		Treatment Period 1												Treatment P1/ P2	Treatment Period 2			Treatment Withdrawal
Visit Name	**Visit 1 (Screening)**	**Visit 2 (Rando-mization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**	**End of Study Visit**	**Early Termination Visit**
Days	**-35 to -2**	**1**	**2 +1**	**4**	**8 ±1**	**15 ±1**	**57 ±3**	**99 ±3**	**127 ±3**	**155 ±3**	**184 ±3**	**198 ±5**	**275 ±5**	**351 ±3**	**366 ±3**	**394 ±7**	**457 ±7**	**549 ±7**	**-**
Weeks	**-5 to -1**	**0**	**0**	**0**	**1**	**2**	**8**	**14**	**18**	**22**	**26**	**28**	**39**	**50**	**52**	**56**	**65**	**78**	**0**
Study drug administration[1]		X									X				X				
Informed consent	X																		
Demography	X																		
Inclusion/ Exclusion criteria	X	X																	
Randomization		X																	
Re-randomization															X				
Medical history	X																		
DXA scan	X										X				X			X	
Lateral spine X-ray	X														X			X	
Physical Examination[8]	X[2]	X		X	X	X	X	X	X	X	X	X	X	X	X[2]	X	X	X[2]	X[2]
Height and weight	X																	X	X
Vital Signs	X	X		X							X	X			X			X	X
Electrocardiogram (ECG)	X	X			X						X				X			X	X
Serum FSH (CZ only)	X																		
Safety laboratory	X	X								X					X			X	X
Urinalysis[3]	X	X								X					X			X	X

Period	Screening		Treatment Period 1												Treatment P1/ P2	Treatment Period 2			Treatment Withdrawal
Visit Name	**Visit 1 (Screening)**	**Visit 2 (Rando-mization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**	**End of Study Visit**	**Early Termination Visit**
Days	**-35 to -2**	**1**	**2 +1**	**4**	**8 ±1**	**15 ±1**	**57 ±3**	**99 ±3**	**127 ±3**	**155 ±3**	**184 ±3**	**198 ±5**	**275 ±5**	**351 ±3**	**366 ±3**	**394 ±7**	**457 ±7**	**549 ±7**	**-**
Weeks	**-5 to -1**	**0**	**0**	**0**	**1**	**2**	**8**	**14**	**18**	**22**	**26**	**28**	**39**	**50**	**52**	**56**	**65**	**78**	**0**
Urine Sediment test[3] (CZ only)	X	X								X					X			X	X
Calcium test[4]	X[5]	X			X	X				X		X		X	X	X		X	X
25 (OH) vitamin D	X	X								X				X			X		
Hepatitis and HIV Screen	X																		
PK blood[6]collection		X		X	X	X	X	X	X	X	X		X		X	X	X	X	X
ADA blood[6]collection		X				X	X	X	X	X	X		X		X	X	X	X	X
PD blood collection[6, 7]		X	X	X			X		X	X	X		X		X	X	X	X	
Injection site reaction		X	X	X	X						X	X			X	X			X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study completion information																		X	X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor.
[1] After all assessments have been performed.
[2] Complete physical examination
[3] Urine sediment test at central lab and local dipstick urinalysis at site
[4] Calcium test refers to calcium and albumin adjusted calcium measurements.
[5] Calcium test has to be repeated at Day -4 (-3) in patients switching from activated vitamin D to natural vitamin D at Visit.
[6] Serum samples may be used for anti-SARS-CoV-2 antibody testing
[7] A minimum of 8 hours fasting is required prior to blood collection and samples have to be collected at the same day time between 7:30 and 10 am.
[8] A Physical Examination will be performed at all visits marked above, however, actual results of the examinations will only be recorded in the eCRF if any clinically significant. medical history or adverse events are identified. Physical Examination was performed or not will only be recorded in the source documents.

Appendix 2: SAS code for multiple imputation analysis

Table 6-1 SAS code for multiple imputation analysis

```
/* Step 1: Achieve Monotone Missing Data Pattern – impute Week 26 values */
PROC MI DATA= transposed_adeff SEED=1 NIMPUTE=25 OUT=adeff_mono;
  BY treatment;
  VAR pchg_wk26 pchg_wk52;
  MCMC IMPUTE=MONOTONE NBITER=5000 NITER =5000;
RUN;
DATA adeff_mono_adj; /* Technical step to add a flag to apply delta adjustment */
  SET adeff_mono;
      Adjusted_arm = 'GP2411';
        IF treatment=Adjusted_arm and COVIDFLG='N' THEN ADJFLG='Y';
        ELSE ADJFLG='N'; OUTPUT;
      Adjusted_arm = 'Prolia';
        IF treatment=Adjusted_arm and COVIDFLG='N' THEN ADJFLG='Y';
        ELSE ADJFLG='N'; OUTPUT;
RUN;
 /* Step 2: Impute under MAR first, then apply delta adjustments for every delta */
%DO i=0 %TO 40;
  %LET shift = - %SYSEVALF(&i/20);
  PROC MI DATA=adeff_mono_adj SEED=1 NIMPUTE=1 OUT=OutMI0;
    BY Adjusted_arm treatment _Imputation_;
    CLASS DXA_type prior_bisphos ADJFLG;
    MONOTONE REG(pchg_wk52);
    VAR DXA_type prior_bisphos baseline pchg_wk26 pchg_wk52;
    MNAR ADJUST (pchg_wk52 / SHIFT=&shift ADJUSTOBS=(ADJFLG='Y'));
  RUN;
  DATA OutMI;  SET OutMI  OutMI0 (in=add);
    IF add THEN Delta = &shift;
  RUN;
%END;
```

Appendix 3: Normal ranges for vital sign parameters

Table 6-2 Normal ranges for vital sign parameters

Vital Signs Parameter (Unit)	Normal range
Systolic blood pressure (mmHg)	90-139
Diastolic blood pressure (mmHg)	45-89
Pulse rate (beats/min)	50-100
Temperature (°C)	35.5-37.4

Appendix 4: Fracture categorization

The following MedDRA preferred terms are considered fractures. Fractures are further (not necessarily distinct) categorized into hip and other non-vertebral fractures.

Table 6-3 Fracture categorization

Type	MedDRA Term	Hip	Other non-vertebral
PT	Acetabulum fracture		Y
PT	Ankle fracture		Y
PT	Atypical femur fracture	Y	
PT	Clavicle fracture		Y
PT	Combined tibia-fibula fracture		Y
PT	Costal cartilage fracture		Y
PT	Craniofacial fracture		Y
PT	Facial bones fracture		Y
PT	Femoral neck fracture	Y	
PT	Femur fracture	Y	
PT	Fibula fracture		Y
PT	Flail chest		Y
PT	Foot fracture		Y
PT	Forearm fracture		Y
PT	Fractured skull depressed		Y
PT	Hand fracture		Y
PT	Hip fracture	Y	
PT	Humerus fracture		Y
PT	Ilium fracture		Y
PT	Jaw fracture		Y
PT	Limb fracture		Y
PT	Lisfranc fracture		Y
PT	Lower limb fracture		Y
PT	Maisonneuve fracture		Y
PT	Osteochondral fracture		Y
PT	Patella fracture		Y
PT	Pelvic fracture		Y
PT	Radius fracture		Y

Type	MedDRA Term	Hip	Other non-vertebral
PT	Rib fracture		Y
PT	Sacroiliac fracture		Y
PT	Scapula fracture		Y
PT	Scapulothoracic dissociation		Y
PT	Skull fracture		Y
PT	Skull fractured base		Y
PT	Sternal fracture		Y
PT	Tibia fracture		Y
PT	Torus fracture		Y
PT	Ulna fracture		Y
PT	Upper limb fracture		Y
PT	Wrist fracture		Y

Sandoz Biopharmaceuticals Clinical Development

GP2411 (INN: denosumab)

Study protocol CGP24112301 / NCT03974100

A randomized, double-blind, multicenter integrated phase I/III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity of GP2411 (proposed biosimilar denosumab) and Prolia® (EU-authorized)

SAP – Post clinical database lock addendum

Sponsor:	Hexal AG, Industriestr. 25, 83607 Holzkirchen, Germany
Date:	03-Aug-2022
Version:	1.0 final
Number of pages:	10

List of abbreviations

%CfB	Percentage change from baseline
ADA	Anti-drug antibody
AUEC	Area under the effect-time curve
CDBL	Clinical database lock
CTX	Carboxy-terminal crosslinked telopeptides of type I collagen
DXA	Dual energy X-ray Absorptiometry
LLOQ	Lower limit of quantification
LS-BMD	Lumbar spine bone mineral density
MedDRA	Medical dictionary for regulatory activities
PD	Pharmacodynamic(s)
PDS	Pharmacodynamics analysis set
PK	Pharmacokinetic(s)
PPS	Per-protocol set
RAS	Randomized analysis set
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA query
TP1	Treatment Period 1
TP2	Treatment Period 2

1 Introduction

This document provides a record of all changes made to the Statistical Analysis Plan (SAP) after final CDBL.

2 Changes to the SAP post-CDBL

The list of changes is provided in the table below.

Table 2-1 List of changes after clinical database lock

Impact	Changes	Rationale for changes
No impact	Appendix 4 (Fracture categorization): "Combined tibia-fibula fracture" preferred term is dropped from non-vertebral fractures.	The term "combined tibia-fibula fracture", has been demoted to a low level term under preferred term "Lower limb fracture" (present in the list of non-vertebral fractures in Appendix 4) in the course of MedDRA 24.1 to 25.0 version transition.
New Table 14.1-2.4, Table 14.2-5.3	In addition to the original PD Analysis Set definition, a sensitivity analysis based on modified (broader) definition will be performed, excluding only patients for whom baseline CTX values might be impaired by a drug effect or for whom CTX baseline values are close to the LLOQ (see Section 2.1).	Exclusion rules which have been defined to minimize the AUEC variability will be removed. Only patients for whom the baseline CTX values might be impaired by the drug effect or for whom CTX baseline values are close to the LLOQ will be excluded from the analysis.
Table 14.1-4.1.1 is updated to include T-score at Screening	T-score for lumbar spine at baseline (original, uncorrected, based on vertebrae exclusions at Screening) is added to Baseline characteristics table based on Safety Set (see Appendix 1)	Eligibility of patients at Screening was based on this criterion (Inclusion criterion 5)
Tables 14.3-1.4, 14.3-1.5 and 14.3-1.6 are updated to include Genant score	Maximum severity grading of vertebral fractures according Genant score is included in Vertebral fractures tables (see Appendix 1)	Genant score is used for grading of vertebral fractures and is relevant information not previously presented
Table 14.3-1.5 is updated	New and worsened vertebral fractures will be checked in the same manner as defined before but comparing with Week 52 Genant scores instead of baseline (see Appendix 1)	Current TP2 table does not allow to see new and worsened vertebral fractures occurring in TP2 only, as a worsening of Genant score in TP1 would still show as worsening of Genant score in TP2 compared to baseline, even if there were no change in Genant score in TP2. Therefore, TP2 table would be more meaningful using a Genant score comparison to Week 52 (last assessment before TP2 start).

New Table 14.3-5.3 Table 14.3-5.4	A new definition of persistent as well as transient ADA is introduced in addition to the old one. A patient had a persistent positive ADA result if: • a positive ADA was detected at the last visit and • there was at least one occasion where positive ADA results were detected at two consecutive available immunogenicity assessments, irrespective of any missing assessments in between them. Transient ADA is still defined as positive but non-persistent. In addition, tables providing immunogenicity results will also be extended (see Appendix 2) in regards of titer results, i.e. titer positives or titer negatives.	The definition for a persistent anti-drug antibody response was refined to reflect the frequent sampling schedule applied in this clinical study to avoid diluting the comparison between drugs due to positive by chance findings. Both the initial and newly defined rule for persistent/transient ADAs are following recommendations provided by Shankar et al (2014) which provides several strategies for defining persistent/transient ADA responses. While for the original definition we define an ADA response as persistent if the last sample of a patient would be ADA positive, this strategy disregards any results obtained before. As in TP1 nine samples over a period of 52 weeks were taken, the definition for a persistent ADA response would also require additional ADA positivity than being only positive at the last visit.
New Table 14.3.1-5 Table 14.3.1-6	Additional tables showing hypersensitivity reactions detected by standardized MedDRA queries (SMQs) “Anaphylactic reaction” and “Hypersensitivity” in TP1 and TP2 are summarized per treatment group (see Appendix 2).	These two SMQs are applied to identify hypersensitivity reactions potentially induced by an immunogenic effect of the study drugs.
New Table 14.1-7.1 Table 14.1-7.2 Table 14.1-7.3	Exposure table split into TP1 and TP2 parts, combined TP1+TP2 table will be done by actual treatment taken in period (see Appendix 2). • Subject-time in TP1 will be calculated as (<date of first dose in TP2 or last visit in TP1 for those who discontinued before> – <date of first dose> +1)/30.25 • Subject-time in TP2 will be calculated as (<date of last visit> – <date of first dose in TP2> +1)/30.25 • Subject-time in TP1+TP2 for all subjects receiving GP2411 will be calculated as the sum of GP2411 subject-time in TP1, GP2411/GP2411 subject-time in TP2 and Prolia/GP2411 subject-time in TP2	Current cumulative table is difficult to understand as time for patients that switched from Prolia to GP2411 (Prolia/GP2411 arm) are still counted and presented under Prolia column.

	• Subject-time in TP1+TP2 for all subjects receiving Prolia will be calculated as the sum of Prolia subject-time in TP1 and Prolia/Prolia subject-time in TP2	
New Table 14.2-1.1.3	Efficacy primary endpoint (Table 14.2-1.1) will be repeated on modified PPS population as a sensitivity analysis (see Appendix 2).	A change in relevant protocol deviations for DXA scans between interim and final CDBL did occur: • New OTH13 protocol deviation at Screening for subject [redacted] -> subject to be excluded in modified PPS • Deletion of OTH10C protocol deviation at Week 52 for subject [redacted] due to correction of Week 52 DXA scan date -> subject to be included in modified PPS

2.1 AUEC of %CfB in serum CTX calculation with less exclusions

Section 2.6.5 of the final SAP v7.0 describes the protocol deviations leading to exclusions from the PDS, and Section 4.8.3 and Section 4.8.4 provide further exclusion criteria related to the validity of CTX samples and AUEC calculation rules. These exclusion criteria aimed to:

- Exclude patients for whom a drug effect on the baseline sample couldn't be ruled out or for whom a drug effect couldn't be determined as CTX baseline values were close to the LLOQ of the CTX assay.
- Minimize the AUEC variability by excluding certain CTX samples and make the availability of a certain amount of CTX samples a prerequisite to calculate the AUEC.

In a sensitivity analysis the AUEC of %CfB in serum CTX will be re-calculated. Excluded CTX samples and/or excluded patients from the PDS will be re-included into the analysis based on a modified PDS. Only patients for whom the baseline CTX values might be impaired by a drug effect or for whom a drug effect couldn't be determined as CTX baseline values were close to the LLOQ of the CTX assay will still be excluded from the analysis.

The rules, which have been defined to minimize the CTX and AUEC variability, will be removed and samples and/or patients included into the analysis as follows:

- Patients with any protocol deviations except EXCL02 (Previous exposure to denosumab) will be included into the analysis
- When CTX values at Visit 3 and 4 and/or Visit 9 and 10 and/or 11 are not available the AUEC will be included into the analysis. Only if baseline (pre-treatment) CTX value is not available then the AUEC of %CfB in serum CTX cannot be calculated.
- If the sampling time window (7:00 am–11:00 am) or the fasting status were violated, the respective CTX sample will still be included in the derivation of AUEC.
- If PK samples at Visit 4, Visit 5 and Visit 6 are < LLOQ, affected patients will be included into the analysis.

The AUEC of %CfB in serum CTX will still be excluded from the analysis, if any impact of a drug effect on the baseline CTX value can't be excluded or if a drug effect couldn't be determined as CTX baseline values were close to the LLOQ of the CTX assay:

- If a patient has EXCL02 (Previous exposure to denosumab) protocol deviation
- If denosumab serum concentrations are unexpectedly >LLOQ in the pre-dose sample.
- If the pre-dose (baseline) CTX sample has been taken after dose administration.
- If the pre-dose (baseline) CTX concentration is <1.24 fold the LLOQ (equal to $0.033\times(1+0.24)=0.04092$) levels.

The statistical analysis of the AUEC will follow the final SAP v7.0 Section 4.6.2.2. For new tables, shells are provided in Appendix 2.

3 Appendices

Appendix 1: Shells for amended outputs

In this Appendix changes to the tables are presented in bold for illustration only (not to be presented bold in programmed outputs).

Table 14.1-4.1.1 Baseline subject characteristics (TP1 SAF)

Characteristic	GP2411 N=xxx	Prolia N=xxx	Total N=xxx
LS-BMD (g/cm^2)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx-xx	xx-xx	xx-xx
FN-BMD (g/cm^2)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx-xx	xx-xx	xx-xx
TH-BMD (g/cm^2)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx-xx	xx-xx	xx-xx
LS T-score			
n	**xxx**	**xxx**	**xxx**
Mean (SD)	**xx.x (x.xx)**	**xx.x (x.xx)**	**xx.x (x.xx)**
Median	**xx.x**	**xx.x**	**xx.x**
Min-Max	**xx-xx**	**xx-xx**	**xx-xx**
CTX (ng/mL)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx-xx	xx-xx	xx-xx
PINP (ng/mL)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx-xx	xx-xx	xx-xx
Prior bisphosphonate use (n (%)			
yes	xx (xx.x)	xx (xx.x)	xx (xx.x)
no	xx (xx.x)	xx (xx.x)	xx (xx.x)

Table 14.3-1.4 Vertebral fractures based on central imaging, TP1 (TP1 SAF)

	GP2411 N=xxx n (%)	Prolia N=xxx n (%)
Number of subjects with at least one vertebral fracture at baseline	xx (xx.x)	xx (xx.x)
Maximum Genant Score		
1	**xx (xx.x)**	**xx (xx.x)**
2	**xx (xx.x)**	**xx (xx.x)**
new vertebral fracture	xx (xx.x)	xx (xx.x)
Maximum Genant Score		
1	**xx (xx.x)**	**xx (xx.x)**
2	**xx (xx.x)**	**xx (xx.x)**
3	**xx (xx.x)**	**xx (xx.x)**
worsening vertebral fracture	xx (xx.x)	xx (xx.x)
Maximum Genant Score		
1	**xx (xx.x)**	**xx (xx.x)**
2	**xx (xx.x)**	**xx (xx.x)**
3	**xx (xx.x)**	**xx (xx.x)**

Table 14.3-1.5 Vertebral fractures based on central imaging, TP2 (TP2 SAF)

	GP2411/GP2411 N=xxx n (%)	Prolia/Prolia N=xxx n (%)	Prolia/GP2411 N=xxx n (%)
Number of subjects with at least one vertebral fracture at **Week 52**	xx (xx.x)	xx (xx.x)	xx (xx.x)
Maximum Genant Score			
1	**xx (xx.x)**	**xx (xx.x)**	**xx (xx.x)**
2	**xx (xx.x)**	**xx (xx.x)**	**xx (xx.x)**
new vertebral fracture	xx (xx.x)	xx (xx.x)	xx (xx.x)
Maximum Genant Score			
1	**xx (xx.x)**	**xx (xx.x)**	**xx (xx.x)**
2	**xx (xx.x)**	**xx (xx.x)**	**xx (xx.x)**
3	**xx (xx.x)**	**xx (xx.x)**	**xx (xx.x)**
worsening vertebral fracture	xx (xx.x)	xx (xx.x)	xx (xx.x)
Maximum Genant Score			
1	**xx (xx.x)**	**xx (xx.x)**	**xx (xx.x)**
2	**xx (xx.x)**	**xx (xx.x)**	**xx (xx.x)**
3	**xx (xx.x)**	**xx (xx.x)**	**xx (xx.x)**

Table 14.3-1.6 Vertebral fractures based on central imaging, TP1+TP2 (TP2 SAF)

Please use the same shell as for Table 14.3-1.4 with Treatment Group Label 3.

Appendix 2: Shells for new outputs

Table 14.1-2.4 Reasons leading to exclusion from modified PD analysis set (TP1 RAS)

Please use the same shell as for Table 14.1-2.3 without PK part

Table 14.1-7.1 Subjects exposure, TP1 (TP1 SAF)

	GP2411 N=xxx		Prolia N=xxx		Total N=xxx	
Dose	Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)
Total	xxx (xx.x)	xx.x	xxx (xx.x)	xx.x	xxx (xx.x)	xx.x
1 dose	xxx (xx.x)	xx.x	xxx (xx.x)	xx.x	xxx (xx.x)	xx.x
2 doses	xxx (xx.x)	xx.x	xxx (xx.x)	xx.x	xxx (xx.x)	xx.x

Subject-time is the sum of each subject's treatment exposure in months, derived as (date of last visit in TP1/first dose in TP2 – date of first dose +1)/30.25

Table 14.1-7.2 Subjects exposure, TP2 (TP2 SAF)

GP2411/GP2411 N=xxx		Prolia/Prolia N=xxx		Prolia/GP2411 N=xxx	
Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)
xxx (xx.x)	xx.x	xxx (xx.x)	xx.x	xxx (xx.x)	xx.x

Subject-time is the sum of each subject's treatment exposure in months, derived as (date of last visit – date of first dose in TP2 +1)/30.25.

Table 14.1-7.3 Subjects exposure, TP1+TP2 (TP1 SAF)

All subjects receiving GP2411 N=xxx		All subjects receiving Prolia N=xxx	
Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)
xxx (xx.x)	xx.x	xxx (xx.x)	xx.x

The 'all subjects receiving GP2411' column includes subjects who switched from Prolia into GP2411 in TP2 and their subject-time in TP2.

Subject-time for all subjects receiving GP2411 is the sum of GP2411 subject-time in TP1, GP2411/GP2411 subject-time in TP2 and Prolia/GP2411 subject-time in TP2.

Subject-time for all subjects receiving Prolia is the sum of Prolia subject-time in TP1 and Prolia/Prolia subject-time in TP2.

Table 14.2-1.1.3 Repeated measures analysis of % CfB in LS-BMD at Week 52 to compare treatments (updated PPS)

Please use the same shell as Table 14.2-1.1.

Table 14.2-5.3 Geometric mean ratio (Test/Reference) and 95% confidence intervals for AUEC of %CfB in CTX (modified PDS)

Please use the same shell as Table 14.2-5.1.

Table 14.3-5.3 Antibody status by time point, TP1 (TP1 SAF)

Visit	Category	GP2411 N=xx n (%)	Prolia N=xx n (%)
Baseline	ADA positive	x (xx.x)	x (xx.x)
	ADA titer positive	x (xx.x)	x (xx.x)
	ADA titer negative	x (xx.x)	x (xx.x)
	NAb positive	x (xx.x)	x (xx.x)
	NAb negative	x (xx.x)	x (xx.x)
	ADA negative	x (xx.x)	x (xx.x)
Visit 6	ADA positive	x (xx.x)	x (xx.x)
	...		
...			
Overall TP1	ADA positive	x (xx.x)	x (xx.x)
	ADA titer positive	x (xx.x)	x (xx.x)
	ADA titer negative	x (xx.x)	x (xx.x)
	NAb positive	x (xx.x)	x (xx.x)
	NAb negative	x (xx.x)	x (xx.x)
	Transient	x (xx.x)	x (xx.x)
	Persistent	x (xx.x)	x (xx.x)
	ADA negative	x (xx.x)	x (xx.x)
...			

'Transient' indicates a subject experiencing a positive ADA result but not qualifying as 'Persistent'.
'Persistent' indicates a subject experiencing a positive ADA result at the final visit and with at least 2 consecutive positive ADA results, irrespective of missing results.

Table 14.3-5.4 Antibody status by time point, TP1+TP2 (TP2 SAF)

Please use the same shell as for Table 14.3-5.3 with Treatment Group Label 3.

Table 14.3.1-5 Hypersensitivity reactions, TP1 (TP1 SAF)

Please use the same shell as for Table 14.3.1-3.1.1

Table 14.3.1-6 Hypersensitivity reactions, TP2 (TP2 SAF)

Please use the same shell as for Table 14.3.1-3.1.1 with Treatment Group Label 3.