SANDOZ A Novartis Division

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Biopharmaceuticals Clinical Development

GP2411

Clinical Trial 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)

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List of abbreviations

%CfB	Percentage change from baseline
25 (OH) vitamin D	25-hydroxyvitamin D
ADA	Anti-drug antibody
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
anti-HBc	anti-Hepatitis B core antibody
anti-HBs	anti-Hepatitis B surface antibody
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUCinf	Area under the serum concentration-time curve extrapolated to infinity
AUEC	Area under the effect versus time curve
BDRM	Blind Data Review Meeting
BMD	Bone mineral density
BUN	Blood urea nitrogen
CFR	Code of Federal Regulation
CI	Confidence interval
Cmax	Maximum serum concentration (of a drug)
CMO & PS	Chief Medical Office and Patient Safety
COA	Clinical outcome assessments
COVID-19	Coronavirus Disease 2019
CRF	Case Report/ Record Form (paper or electronic)
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTX	Collagen C-telopeptide
CV	Coefficient of variation
CZ	Czech Republic
dL	Deciliter
DXA	Dual energy X-ray Absorptiometry
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FN-BMD	Femoral neck bone mineral density

FSH	Follicle-stimulating hormone
g	Gram
GCP	Good Clinical Practice
GCS	Global Clinical Supply
h	Hour
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
INN	International Nonproprietary Names
INR	International Normalized Ratio
IOF	International Osteoporosis Foundation
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
JP	Japan
kDa	Kilodalton
kg	Kilogram(s)
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
LS-BMD	Lumbar spine bone mineral density
LSM	Least-squares means
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
mL	Milliliter(s)
MMRM	Mixed-model repeated measures
NAb	Neutralizing antibodies
NCI	National Cancer Institute
ng	Nanogram(s)
NYHA	New York Heart Association (Functional Classification)
ONJ	Osteonecrosis of the jaw
PD	Pharmacodynamic(s)
PDS	Pharmacodynamics analysis set
PFS	Pre-filled syringe
PINP	Procollagen I N-terminal propeptide
PK	Pharmacokinetic(s)

PKS	PK analysis set
PMDA	Pharmaceuticals and Device Agency
PMO	Postmenopausal osteoporosis
PPS	Per-Protocol Set
PT	Prothrombin time
QMS	Quality Management System
RANK	Receptor Activator of Nuclear factor Kappa-B
RANKL	Receptor Activator of Nuclear factor Kappa-B Ligand
s.c.	Subcutaneous
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TH-BMD	Total hip bone mineral density
TP1	Treatment Period 1
TP2	Treatment Period 2
WBC	White blood cell(s)
WHO	World Health Organization
µL	Microliter

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/ time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest and who has consented to participate in this study
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Screen Failure	A patient who did not meet one or more criteria that were required for participation in the study
Study completion	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study medication	Any drug administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Withdrawal of consent	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Amendment 6 (released on 30-Oct-2020)

Amendment rationale

The purpose of this amendment is to address the following:

- Implement FDA´ advice information request on Investigational New Drug application (IND 135707) dated 30-Apr-2020 on missing data
- Evaluation of the impact of the COVID-19 pandemic including retrospective serological testing for SARS-CoV-2 antibodies may be performed. This is to assure data robustness through potential sensitivity analyses for LS-BMD, PK and PD and adverse events reporting to assess a possible impact from SARS-CoV-2 on these endpoints
- Update of statistical testing strategy from one overall study testing strategy to three separate testing strategies to address different health authority requirements

Furthermore, editorial changes were made to correct inconsistencies within this protocol.

Study status

At the time of this protocol amendment, the study has finished recruitment with overall 527 patients enrolled globally.

Main Changes to the protocol

Changes based on FDA feedback on missing data

- Inclusion of more details for MMRM model in Section 12.5.2.1
- Inclusion of summary statistics on missing data patterns in Section 12.5.3
- Additional details on missing data handling for the primary analysis of %CfB in LS-BMD in Section 12.5.3.1
- Inclusion of training provided to the investigators for prevention of missing data in Section 11.3
- Inclusion of laboratory normal range for albumin in Section 5.2
- Inclusion of sensitivity analysis to assess robustness of MAR assumption for MMRM primary analysis of %CfB in LS-BMD in Section 12.5.4

Changes related to COVID-19 pandemic

- Risk assessment related to COVID-19 due to study medication included in Section 4.5 Risks and Benefits
- Included retrospective serological testing for SARS-CoV-2 antibodies may be performed in Section 8.5.2
- Updated Table 8-1 assessment schedule
- [redacted]

Other changes

Update of use of research results (data) collected for study evaluation prior to withdrawal of informed consent in Section 9.1.2

Statistical testing strategy updated from one overall testing strategy in the study to three separate testing strategies to address different health authority requirements

- Reference to detailed testing strategy included in Section 12
- Testing strategy details updated in Section 12.5.2

Description of summary statistics moved to statistical introduction section to ensure applicability and consistency across sub-sections

- Inclusion of description of summary statistics in Section 12
- Removal of description of summary statistics in Sections 12.2, 12.6.3 and 12.6.4
- Removal of summary statistic of frequency of concentrations below LLOQ in Section 12.6.3 and 12.6.4

Clarification on missing or duplicated summary statistics

- Inclusion of summary statistics of AUEC of %CfB in CTX concentrations after the first dose in Section 12.5.2.2
- Inclusion of summary statistics of AUCinf and Cmax in Section 12.5.2.3
- Removal of repeated summary statistics of PD concentrations in Section 12.6.4

Clarification of assignment of analyses as sensitivity, supportive or supplementary analysis in Sections 12.5.2.1, 12.5.4, 12.5.5, and 12.8.4.

Specification of sensitivity analyses to assess impact of stratification errors in Section 12.1 moved to statistical analysis plan.

Move of PD analysis description to PD section

- Move of handling of CTX concentrations below LLOQ in summary statistics from Section 12.5.3 to Section 12.6.4
- Move of PD secondary endpoint description from Section 12.6.1 to Section 12.6.4

Focus of laboratory safety analysis by grade on low/ normal/ high classification instead of CTCAE grading in Section 12.6.2

Specification of ECG analyses in Section 12.6.2

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

This amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities (HA) for approval or notification as required according to local regulations. The changes described in this amended protocol are substantial.

Amendment 5 (released on 21-Feb -2020)

Amendment rationale

The purpose of this amendment is to address the following:

- Changes requested by FDA and other updates in the data analysis section: FDA advice on Investigational New Drug application (IND 135707) of 25-Jul-2019 following the second review of the protocol v02 (released on15-Mar-2019). This also led to clarifications of other statistical topics including overall study testing strategy.
- Changes of calcium assessment: To further ensure the safety of patients, exclusion criterion #15 is updated; allowing only patients with normal albumin values to enter into the study. As a consequence, the assessment of calcium levels is shifted from the parameter serum albumin adjusted calcium to the parameter serum calcium (equals total serum calcium) throughout the entire study.
- The vitamin D repletion and the processing time for the central laboratory samples could take more than 28 days. To avoid unnecessary repeated DXA and blood sampling for rescreening, the screening period is extended from 28 days to 35 days. Patients with vitamin D deficiency are allowed to be treated at the investigator's discretion with an appropriate vitamin D dose in addition to the per protocol scheduled vitamin D supplementation during the screening period.

The changes in local amendments 3 (for Czech Republic, released on 28-Jun-2019) and local amendment 4 (for Japan, released on 10-Sept-2019) are added in this global amendment 5; and editorial changes are made to correct inconsistencies within the protocol.

Study status

At the time of this protocol amendment, the study has recruited more than 200 patients globally.

Changes to the protocol

Changes Requested by FDA

Analysis set for primary analysis of percentage change from baseline (%CfB) in lumbar spine bone mineral density (LS-BMD) for FDA and PMDA is changed from per protocol set (PPS) to treatment period 1 full analysis set (TP1 FAS) in Section 12.5:

- Analysis set for the primary analysis of %CfB in LS-BMD was updated from PPS to TP1 FAS including now all patients with at least one post-baseline LS-BMD value (including Week 26 assessment)

Reduction of sample size from 522 patients to 492 patients in Section 3, Section 5 and Section 12.8:

- Following a change in primary analysis set from PPS to TP1 FAS the drop-out rate was adjusted from 25% to 15%.
- In addition, SD estimate of %CfB in LS-BMD at Week 52 was updated from 3.96 to 4.08 deriving the SD as pooled SD over the 3 historical published trials instead of using weights based on variance of difference in mean between denosumab and placebo.

Modification of TP1 FAS in Section 12.1:

- Analysis set definition of TP1 FAS was narrowed down to have at least one available post-baseline LS-BMD value regardless of available post-baseline PD or PK values.

Change of primary analysis set for %CfB in LS-BMD in Section 12.5 and Section 12.8.4:

- For FDA and PMDA primary analysis set was changed from PPS to TP1 FAS with PPS as sensitivity analysis.
- Following a decrease in sample size the power for the sensitivity analysis on PPS using a (-1.45, 1.45) margin was estimated to be at least 84%.

Clarification of rationale for different stratification factors in Protocol summary, Section 6.3.2 and Section 12.5.2:

- Rationale for each stratification factor was provided in more detail to allow for a more in-depth understanding on why stratification factors were implemented and in which endpoint analysis they need to be accounted for.
- For the primary analysis of %CfB in LS-BMD prior bisphosphonate use (yes/ no) was included into the model as a potential source of heterogeneity that cannot be assured to be completely controlled through the use of inclusion/exclusion criteria. Age group (<65 years/ ≥65 years) was removed from the model as age can best be assumed to have a linear effect on LS-BMD 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.

Changes of calcium assessment

The following changes in the reporting of calcium values were implemented:

- The assessment of calcium values throughout the study was shifted from “albumin adjusted serum calcium” to “calcium”.
- Cut-off values for hypocalcemia and hypercalcemia were added in exclusion criterion #15 in Protocol Summary and Section 5.2:
  - Hypocalcemia was defined as calcium less than 2.10 mmol/L [8.42 mg/dL].
  - Hypercalcemia was defined as calcium more than 2.62 mmol/L [10.50 mg/dL).
- The same cut-off values are applied for the evaluation of the adverse events hypocalcemia and hypercalcemia.
- SI and conventional units are both provided for calcium test as well as other laboratory parameters.

Other main changes

Screening period was prolonged from 28 days to 35 days in Figure 3-1, Table 8-1, Section 3 and Section 8.1.

Clarification on safety laboratory assessments:

- Wordings were updated in Section 8.5.

Clarification on retest of vitamin D during the screening was added:

- Exclusion criterion #14 in Protocol Summary and Section 5.2.

Clarification on repletion of calcium during the screening was added:

- Exclusion criterion #15 in Protocol Summary and Section 5.2.
- Section 8.5.2, repletion rules were specified

Clarification on safety lab values:

- SI reference values were added in Section 5.2.

A +1 day window was added to Visit 3 to facilitate site visit schedules in Table 8-1.

Clarification on analytical method for pharmacokinetics:

- Wordings were updated in Section 8.4.2.

Further unblinded sponsor staff was specified in Section 6.4:

- Compliance Clinical Operations staff was added

Clarification on physical examination:

- Documentation of physical examination in eCRF was specified in Table 8-1 and Section 8.5.1

Clarification of purpose of interim analysis in Section 4.4 and Section 12.7:

- Purpose of interim analysis was clarified to provide an early read-out of the primary analyses without affecting validity of subsequent analyses.

Clarification of hierarchical testing strategy in Section 12.5.2:

- With different HAs requiring testing of different primary endpoints, the overall study testing strategy was clarified.

Change of layout of description of testing requirements for different HAs in Section 12:

- To avoid duplication and ensure no misunderstanding testing requirements for different HAs are now presented in tabular format.

Removal of description of application of analysis set from Section 12.1:

- To avoid duplication and potential inconsistency application of different analysis sets is now described in Sections 12.5 and 12.6 only.

Removal of reference to BDRM in Section 12.1:

- Sponsor internal data review process was adapted to an ongoing blind data review instead of a single blind data review meeting (BDRM) before database lock. Protocol deviations leading to exclusion will be defined in the SAP version finalized before database lock.

Implementation of analysis set TP2 RAS in Section 12.1:

- Patient disposition for patients re-randomized to TP2 will be presented for all patients re-randomized to TP2 regardless of any post-baseline efficacy, PD or PK value, requiring the implementation of a new analysis set.

Removal of description of non-mandatory listings in Section 12.5 and Section 12.6:

- Scope of non-mandatory listings will be defined in the SAP with related documents and was removed from protocol.

Removal of sensitivity analysis on TP1 FAS for PK and PD endpoints in Sections 12.5 and Section 12.6:

- Sensitivity analysis on TP1 FAS for PK and PD endpoints was deemed to be of limited value given the decreased accuracy in deriving parameters with missing values or relevant protocol deviations and was therefore removed from the protocol.

Harmonization of description of analysis sets in Section 12.1:

- Description of analysis sets was aligned to use the same wording when the same criteria was to be met.
- Clarification was provided that for analyses on the TP1 FAS patient would be allocated to the strata as randomized in the IRT and not as stored in the clinical database.

Removal of description of margin for CTX in Section 12.8:

- For equivalence testing on PD endpoint AUEC of %CfB in CTX after first dose the standard bioequivalence margin of (0.80, 1.25) will be used with no study specific adaptions and therefore confusing statement removed from protocol.

Clarification on Trial Feedback Questionnaire (TFQ) in Section 8.6.1:

- Sentence on transfer of any spontaneous information on AE to safety database removed as not applicable, i.e. no option to enter free text in the TFQ.

Local Amendment 4 (released on 10-Sep-2019) for Japan only

Amendment rationale

The purpose of this amendment is to address the feedback from Pharmaceuticals and Medical Devices Agency (PMDA) deficiency letter on CGP24112301 Clinical Trial Notification received on 23-Aug-2019, 03-Sep-2019 and 09-Sep-2019. Changes in the protocol based on local amendment 4 are applicable for Japan only.

Natural vitamin D was specified in the following section:

- Additional study treatment in Section 6.1.2.

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

- Protocol summary, Key exclusion criteria
- Exclusion criterion #8 in Section 5.2.
- Prohibited medication in Section 6.2.2.

An additional laboratory test at Day -4 was added for testing of albumin adjusted serum calcium levels in Japanese patients switching from activated vitamin D to natural vitamin D at Visit 1 in the Assessments Schedule, Table 8-1 and screening, Section 8.1.

Japanese brand name was added to the respective sections.

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

Amendment rationale

The purpose of this local amendment is to respond to the deficiency letter (sukls99642/2019) issued by Czech Republic Health Authority on 6-Jun-2019. Changes in the protocol based on local amendment 3 will be implemented in the Czech Republic only.

Inclusion criterion #2 in Section 5.1

- A test for serum follicle-stimulating hormone (FSH) to confirm menopause at Screening was added to inclusion criterion #2.
- Table 8-1 Assessment Schedule was updated to include the FSH test

Laboratory evaluations in Section 8.5.2

- Urine sediment test by microscopy was added at regular intervals
- Screening in Section 8.1 was updated to include the urine sediment test

Amendment 2 (released on 15-Mar-2019)

Amendment rationale

The main purpose of this amendment is to respond the feedback from the European Medicines Agency (EMA) follow-up scientific advice of 13-Dec-2018 and Food and Drug Administration (FDA) advice on investigational drug application (IND 135707) of 06-Feb-2019 following their review of the study protocol.

In addition, severity grading of adverse events, which was not defined by the Common Terminology Criteria for Adverse Events (CTCAE) classification is clarified. Severity grading of injection site reactions was updated to align with the CTCAE classification. The communication guideline of immunogenicity results was specified.

Furthermore, editorial changes were made to correct inconsistencies within this protocol.

Study Status

At the time of this protocol amendment, the study has not yet started.

Changes to the protocol

Requested changes from Health Authorities (EMA and FDA)

Increase of sample size in Section 12:

- The sample size calculations were updated to change the confidence interval for the LS-BMD for the FDA requirements to use a 95% confidence interval (previously a 90% confidence interval) in the similarity assessment of the primary endpoint. This results in a change in the total sample size from 436 to 522 throughout the protocol (Figure 3-1 was updated).

Inclusion criterion #5 in Section 5.1:

- The regions, total hip and femoral neck, were removed for BMD measurement to assess patient eligibility; inclusion will be based solely on LS-BMD in terms of T-score. This is in line with the fact that the study primary endpoint is based on a percent change from baseline in BMD specifically at the lumbar spine.

Additional exclusion criterion #6 in Section 5.2:

- Exclusion of patients with active healing fractures was added.

Exclusion criterion #7 in Section 5.2:

- Washout period for previous tibolone, oral or transdermal estrogen and selective estrogen receptor modulators, was extended from 6 months to 12 months prior to screening.

Additional study treatment in Section 6.1.2:

- For calcium and vitamin D supplementation, dosage as per investigator discretion has been replaced with at least 1000 mg of elemental calcium and 800 IU vitamin D supplementation daily from screening until the end of the study.

DXA assessment in Section 8.3.1:

- DXA assessments of hip joint (total hip and femoral neck) were standardized in terms of using the same side of the body (left).

Assessment of nonvertebral fractures in Section 8.5.4:

- Instruction to use local radiology report for nonvertebral fractures was added.

Study discontinuation and completion in Section 9.1.1 and Section 9.2:

- The recommendation for transitioning patients to alternative antiresorptive osteoporosis therapy was further emphasized.

Safety monitoring and reporting in Section 10.1.3:

- Reporting of all potential serious risks to the FDA in accordance with 21 CFR 312.32 (c) was specified.

Stratification factor of "prior bisphosphonate use" added:

- Prior bisphosphonate use (oral and parenteral route) was added to the stratification scheme to account for potential study population heterogeneity due to this prior therapy (changes in Section 3 Study design; Section 6.1.3 Treatment arms/groups; Section 6.3.2 Treatment assignment, randomization; and Section 12.5.2 Statistical model, hypothesis, and method of analysis).
- With the introduction of an additional stratification factor, the list of factors and covariates in the statistical models has been carefully reconsidered and updated to avoid possible model instability through confounding. The primary analysis will not include region in the statistical model. This model should provide a stable main analysis, which is robust to any possible imbalances. A separate sensitivity analysis will be conducted to demonstrate homogeneity of the regions (LS-BMD and AUEC CTX).

PK and ADA sampling time point at Week 22 added:

- A PK sampling time point at Week 22 was added to better capture the PK profile. An ADA sampling time point at Week 22 was also added to ensure that an ADA sample is obtained at every sampling time point in line with PK sampling, (changes in Table 8-1 Assessment schedule; Section 8.4.1 Pharmacokinetics blood sample collection and handing; Section 8.5.3.1 Immunogenicity blood sample collection and handling).

PD sampling time point at Day 2 added:

- A PD sampling time point at Day 2 was added to better capture the PD profile (changes in Table 8-1 Assessment schedule (all visit numbers were updated accordingly); Section 8.3.2.1 Biomarker blood sample collection and processing.

PD comparability index removed:

- The PD comparability index may not be powerful to detect differences between test and reference product, therefore this approach was deleted from the protocol (change in Section 12.5.4 Sensitivity and Supportive analyses).

AUEC clarification:

- The AUEC definition was refined as the area under the baseline using all evaluable time points after the first 60 mg s.c. dose until CTX values return and cross the baseline for the first time, without including any rebound effects (specification on AUEC calculation in Section 12.4 Pharmacokinetics and pharmacodynamics). The rebound area has been included as sensitivity analyses in Section 12.5.4.

Definition of analysis sets in Section 12.1:

- A new analysis set, Randomized Analysis Set (RAS), which included all randomized patients whether they are treated or not was added. The RAS will be used for disposition tables to include all patients who were randomized.
- The Treatment Period 1 Full Analysis Set (FAS) definition in Section 12.1 was updated to include only patients who received at least one treatment with study medication and for whom there is some efficacy or PD data available.
- The Per Protocol Set (PPS) definition in Section 12.1 was split into two analysis sets: an efficacy PPS which focuses on the protocol adherence, related to the LS-BMD measurements and safety, and a Pharmacodynamics (PD) analysis set (PDS) which focuses on the protocol adherence, related to the CTX measurements and safety.

Clarification of handling of missing percent change from baseline (%CfB) LS-BMD values in the efficacy primary analysis:

- A clarification on the handling of missing %CfB LS-BMD values was added in Section 12.5.3 for the efficacy primary analysis. It is further clarified that a sensitivity analysis will be provided which does allow for the inclusion of patients with missing LS-BMD values in Section 12.5.4.

Margin justification was clarified in Section 12.8.2:

- For clarification, the wording for the margin justification was updated to "A margin of 1.45% retains at least 70% of the minimum treatment effect (FDA approach)".

Clarification on grading of adverse events by CTCAE

Injection site reactions in Section 8.5.5:

- Instruction to grade the severity of injection site reactions was updated according to the CTCAE classification in Table 8-3.

Adverse events in Section 10.1.1:

- The severity grading was introduced for adverse events, which were not defined by the CTCAE classification.

Inclusion of the immunogenicity results communication guidance

- The instruction on the communication of immunogenicity results was added in Section 8.5.3.1.

Editorial changes

Study design in Section 3:

- Visit number 15 instead of 13 for Week 52 was corrected.

Population in Section 5:

- Inclusion criterion #6 was updated for clarification of X-ray.
- Exclusion criterion #7 was updated to cross reference to exclusion criterion #25.

Investigational and comparator drugs in Section 6.1.1:

- Polysorbate 20 concentration was corrected to 0.01% in Table 6-1.

Screening in Section 8.1:

- ECG assessment was added to be consistent with Table 8-1.

Pharmacokinetics in Section 8.4:

- For clarification previous pharmacokinetics Section 8.5.2 moved to Section 8.4. Consequently, all subsequent subsections under Section 8 were renumbered.

Appropriateness of pharmacokinetic measurements in Section 8.4.3:

- PK assessment justification was added.

Laboratory evaluations in Section 8.5.2:

- Out of range laboratory values evaluations were further specified.
- Hypocalcemia evaluation is further clarified.

Immunogenicity in Section 8.5.3:

- Immunogenicity risk of study drugs was specified.

Pregnancy and assessment of fertility in Section 8.5.7:

- Wording was updated to be consistent with Section 10.1.4 Pregnancy reporting.

Data analysis and statistical methods in Section 12:

- The confidence interval for the PK endpoint for PMDA was corrected to 90.
- For readability, the terminology of the natural logarithm function “ln” was replaced by “log” throughout the protocol. Log was added to the list of abbreviations to make it clear that the natural logarithm is still meant.

Pharmacokinetics and pharmacodynamics in Section 12.4:

- The PK and PD parameters were moved to the newly introduced Section 12.4 Pharmacokinetics and pharmacodynamics. Consequently, all subsequent subsections under Section 12 were renumbered.

Handling of missing values/ censoring/ discontinuations in Section 12.5.3:

- It is now specified that the visit windows that will lead to exclusion from analysis set will be defined in the Blinded Data Review Meeting.
- An explanation how to handle LLOQ values for the PK and PD parameter calculation was provided.

Efficacy endpoints in Section 12.6.1:

- Fracture rates were moved from the efficacy endpoints for Treatment Period 1 and Treatment Period 2 and became part of the safety assessments

Safety endpoints in Section 12.6.2:

- Specification of what laboratory outputs are to be provided was clarified.

Pharmacokinetics in Section 12.6.3:

- Clarification that the ratio of geometric means with associated confidence intervals will be provided as a secondary PK endpoint relevant for EMA only.

Pharmacodynamics in Section 12.6.4:

- More details on the bioequivalence assessment of the secondary PD endpoint have been provided.

Amendment 1 (released on 10-Dec-2018)

Amendment rationale

The amendment is to address the request for information from the US Food and Drug Administration (FDA) based on the GP2411 Investigational New Drug review (submitted 30th-Nov-2018). The main purpose of this amendment is editorial changes to ensure the correct terminology is appropriately used when referring to US-licensed Prolia and EU-authorized Prolia as well as the regulatory determination of "highly similar", which will be made by the FDA at a later time.

Study status

At the time of this protocol amendment, the study has not yet started.

Changes to the protocol

Section 4.5 Risks and benefits:

- Section was edited to reflect the appropriate use of wording to describe the results of comparative analytical studies for GP2411.

Throughout this clinical protocol, wording has been edited to ensure the appropriate terminology is used when referring to US-licensed Prolia and EU-authorized Prolia or in general, to biosimilar development:

- The term "originator" product has been implemented throughout this protocol where appropriate to refer in general to biosimilar development.
- US-licensed Prolia and EU-authorized Prolia are used (together or separately) when more specific detail is necessary with regard to GP2411 and this study.
- The term "comparator" is used to refer to EU-authorized Prolia that is used in this study.

Protocol summary

Protocol number	CGP24112301
Full Title	A randomized, double-blind, multicenter integrated phase I/III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity of GP2411 (proposed biosimilar denosumab) and Prolia® (EU-authorized)
Brief title	Study investigating PK, PD, efficacy, safety, and immunogenicity of biosimilar denosumab (GP2411) in patients with postmenopausal osteoporosis
Sponsor	Hexal AG, Industriestr. 25, 83607 Holzkirchen, Germany Sandoz Inc., 100 College Road West, Princeton, NJ 08540, USA (for US)
Investigation type	Biosimilar
Study type	Interventional
Study phase	Integrated Phase I/III
Purpose and rationale	The purpose of this study is to demonstrate similar PK, PD, efficacy, safety, and immunogenicity of GP2411 and EU-authorized Prolia for up to 52 weeks in postmenopausal women with osteoporosis, following two 60 mg subcutaneous injections every 6 months. The study also involves a transition from EU-authorized Prolia to GP2411 for 50% of the patients on EU-authorized Prolia at Week 52, with a subsequent evaluation of safety and immunogenicity for 26 weeks after the transition.
Primary Objective(s)	To demonstrate similar PK, PD and efficacy between GP2411 and EU-authorized Prolia, the following sets of primary endpoints have been defined following scientific consultations with health authorities in Europe (EMA), US (FDA) and Japan (PMDA): • EMA requirement: (a) percent change from baseline (%CfB) at Week 52 in lumbar spine bone mineral density (LS-BMD) (b) area under the effect versus time curve (AUEC) after the first dose of %CfB in serum collagen C-telopeptide (CTX) • FDA and PMDA requirements: %CfB in LS-BMD at Week 52 • PMDA requirement: PK similarity AUCinf and Cmax between GP2411 and Prolia after the first dose
Secondary Objective(s)	**Key Secondary Objective:** To demonstrate PD similarity in terms of serum CTX response between GP2411 and EU-authorized Prolia: • FDA and PMDA requirements: AUEC after the first dose of %CfB in serum CTX **Secondary Objectives:** **Treatment Period 1 (Day 1 - Week 52)** To further compare GP2411 and EU-authorized Prolia in terms of PK, PD, efficacy, safety, and immunogenicity with respect to the following criteria: • BMD: %CfB in lumbar spine, femoral neck and total hip BMD (LS-BMD, FN-BMD, TH-BMD) at Week 26

	• BMD: %CfB in femoral neck and total hip BMD (FN-BMD, TH-BMD) at Week 52 • PD markers: CTX and procollagen I N-terminal propeptide (PINP) serum concentrations until Week 52 • Safety: Fractures, vital signs, laboratory safety assessments, injection site reactions, ECG, occurrence of adverse events and serious adverse events, up to Week 52 • Immunogenicity: Development of binding and neutralizing anti-drug antibodies (ADAs) until Week 52 • Serum PK parameters AUCinf and Cmax after the first dose (EMA only) • Denosumab serum concentrations until Week 52 **Treatment Period 2 (Week 52 - Week 78):** To further evaluate and compare GP2411 and EU-authorized Prolia in terms of PK, PD, efficacy, safety and immunogenicity with respect to the following criteria, after transitioning 50% patients from EU-authorized Prolia to GP2411: • BMD: %CfB in lumbar spine, femoral neck and total hip BMD (LS-BMD, FN-BMD, TH-BMD) at Week 78 • PD markers: CTX and PINP serum concentrations from Week 52 to Week 78 • Safety: Fractures, vital signs, laboratory safety assessments, injection site reactions, occurrence of adverse events and serious adverse events, from Week 52 up to Week 78 • Immunogenicity: Development of binding and neutralizing ADAs from Week 52 to Week 78 • Denosumab serum concentrations from Week 52 to Week 78
Study design	This is a multicenter, randomized, parallel arm, double-blind study with a total duration up to 82 weeks. Approximately 492 postmenopausal patients with osteoporosis will be randomized. Randomization will be stratified by region (US, Rest of World, Japan), age group (<65 years/ ≥65 years) and prior bisphosphonates use (yes/ no) and body weight group (<70 kg/ ≥70 kg). The Screening Period of up to 5 weeks will assess patient's eligibility. At the beginning of Treatment Period 1, eligible patients will be randomized using a 1:1 ratio to one of the two treatment groups: GP2411 or EU-authorized Prolia. All randomized patients will receive either 60 mg GP2411 or 60 mg EU-authorized Prolia on Day 1 and at Week 26. At the beginning of Treatment Period 2, which starts from Week 52, all patients still in the study will be allocated the treatment for Treatment Period 2 through the IRT in a blinded manner. Patients in Treatment Period 1 Prolia group will be re-randomized 1:1 to either continue with a third dose of EU-authorized Prolia, or transition to GP2411. All patients in the GP2411 group will continue the treatment with a third dose of GP2411. Thus, effectively in Treatment Period 2, the three groups "GP2411", "Prolia" and "Transition from Prolia to GP2411" are distributed in an approximate 2:1:1 ratio. PK, PD, efficacy, safety and immunogenicity will be evaluated until the end of study at Week 78.
Population	Postmenopausal women diagnosed with osteoporosis, aged ≥55 and ≤80 years, with a body weight ≥50 and ≤90 kg

Key Inclusion criteria	• Postmenopausal women, diagnosed with osteoporosis. Postmenopausal status is defined as at least 12 consecutive months of amenorrhea prior to date of screening, for which there is no other obvious pathological or physiological cause. [For CZ only: Postmenopausal status is defined as at least 12 consecutive months of amenorrhea prior to date of screening for which there is no other obvious pathological or physiological cause and by elevated serum follicle-stimulating hormone (FSH) level assessed by central laboratory at screening] • Aged ≥55 and ≤80 years at screening • Body weight ≥50 kg and ≤90 kg at screening • 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 • At least two vertebrae in the L1-L4 region (vertebrae to be assessed by central reading of lateral spine X-ray during the Screening Period) and at least one hip joint are evaluable by DXA

Key Exclusion criteria	• Previous exposure to denosumab (Prolia/ Pralia in Japan, Xgeva/ Ranmark in Japan, or biosimilar denosumab)
	• History of hypersensitivity to any recombinant protein drugs or any of the excipients used in GP2411 or Prolia
	• History and/or presence of one severe or more than two moderate vertebral fractures (as determined by central reading of lateral spine X-ray during the Screening Period)
	• History and/or presence of hip fracture
	• Presence of active healing fracture according to assessment of investigators
	• History and/or presence of bone metastases (see also exclusion criterion #25), bone disease or metabolic disease (except osteoporosis) that may interfere with the interpretation of the results, e.g. Paget's disease, rheumatoid arthritis, ankylosing spondylitis, osteomalacia, osteogenesis imperfecta, osteopetrosis, Cushing's disease, hyperprolactinemia or malabsorption syndrome
	• Ongoing use of any osteoporosis treatment (other than calcium and vitamin D supplements). Following rules for wash-out periods for osteoporosis treatments have to be adhered to:
	• Drugs being investigated for osteoporosis: dose received at any time
	• Romosozumab: dose received at any time
	• Strontium or fluoride (for osteoporosis): dose received at any time
	• Intravenous bisphosphonates: dose received within 5 years prior to screening
	• Oral bisphosphonates
	  • >3 years of cumulative use prior to screening
	  • any dose received within 12 months prior to screening
	• Teriparatide or any PTH analogs: dose received within 12 months prior to screening
	• Tibolone, oral or transdermal estrogen, selective estrogen receptor modulators: dose received within 12 months prior to screening

	• Calcitonin: dose received within 6 months prior to screening
	• Cinacalcet: dose received within 3 months prior to screening
	• 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
	• Other bone active drugs, including anti-convulsives (with the exception of benzodiazepines), heparin, systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin releasing hormone agonists, anabolic steroids, within the past 3 months before screening
	• Oral or dental conditions:
	  • osteomyelitis or history and/or presence of osteonecrosis of the jaw (ONJ)
	  • presence of risk factors for ONJ (e.g. periodontal disease, poorly fitting dentures, invasive dental procedures such as tooth extractions in 6 months before screening)
	  • active dental or jaw condition which requires oral surgery
	  • planned invasive dental procedure
	• Current uncontrolled status of hypothyroidism or hyperthyroidism
	• History and/or current hypoparathyroidism or hyperparathyroidism, irrespective of current controlled or uncontrolled status
	• Vitamin D deficiency (25 [OH] vitamin D serum level <50 nmol/L [<20 ng/mL]). Appropriate vitamin D dose in addition to vitamin D supplementation is permitted at the investigator's discretion and patients will be retested during the screening period or may be rescreened (refer to Section 8.1)
	• Current hypocalcemia, defined as calcium <2.10 mmol/L [<8.42 mg/dL]) or hypercalcemia, defined as calcium >2.62 mmol/L [>10.50 mg/dL]; patients must have normal albumin values (32 – 55 g/L [3.2-5.5 g/dL]) according to central laboratory normal range. (Refer to Section 8.5.2 for specifications on repletion of calcium during the screening period).

Study medication	EU-authorized Prolia® pre-filled syringe (PFS) or GP2411 PFS
Efficacy assessments	LS-BMD, FN-BMD, TH-BMD as assessed by DXA will be measured at baseline, Week 26, 52, and 78.
Pharmacodynamic assessments	Serum CTX and PINP concentrations will be measured at time points specified in the assessment schedule.
Pharmacokinetic assessments	Serum denosumab concentrations will be measured at time points specified in the assessment schedule.
Key safety assessments	• Occurrence of fractures • Incidence of adverse events • Laboratory assessments • Vital signs • ECG • Anti-drug antibodies (ADA)
Data analysis	To evaluate the primary objectives

	• For LS-BMD a mixed model repeated measures (MMRM) will be fitted using the %CfB measurements at Week 26 and Week 52. The MMRM model will include treatment (GP2411, Prolia), prior bisphosphonate use (yes/ no), DXA machine type (Lunar/ Hologic machine), time (visits Week 26, Week 52) and the interaction between time (visits Week 26, Week 52) and treatment (GP2411, Prolia) as fixed factors. Baseline LS-BMD value will be included as a continuous covariate. • For the log-transformed AUEC (i.e. log(AUEC)) of the %CfB in CTX after first dose an analysis of covariance (ANCOVA) will be performed. The ANCOVA model will include treatment as fixed effect and baseline CTX as a continuous covariate. CIs for the least-squares mean differences in %CfB LS-BMD and in log(AUEC) of %CfB in serum CTX will be estimated from their respective models. CI for the ratio of the geometric mean AUEC of %CfB in serum CTX will then be calculated by anti-log transformation of the CI of the difference in log(AUEC). • For each of the log PK parameters (AUCinf and Cmax) an ANCOVA will be fitted which will include treatment as fixed factor and weight as continuous covariate. CI for the ratio of the geometric mean of the PK parameters will be calculated by anti-log transformation of the CI of the difference in the log PK parameters. The primary objective is considered met if: 1. For EMA requirement: the 95% CI for the difference in %CfB for LS-BMD has to be completely contained within the equivalence interval of [-2.00%, 2.00%] and the 95% CI for the ratio of the geometric mean AUEC of %CfB in serum CTX has to be completely contained within the equivalence interval of [0.80, 1.25]. 2. For FDA requirement: the 95% CI for the difference in %CfB for LS-BMD has to be completely contained within the equivalence interval of [-1.45%, 1.45%]. 3. For PMDA requirement: the 95% CI for the difference in %CfB for LS-BMD has to be completely contained within the equivalence interval of [-2.00%, 2.00%] and the 90% CI for the ratio of the geometric means of denosumab serum Cmax and AUCinf have to be completely contained within the equivalence interval of [0.80, 1.25]. 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. Summary statistics for continuous variables will include the number of non-missing observations, mean, standard deviation (SD), minimum, median, and maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute (n) and relative frequencies (%). For AUEC of %CfB in serum CTX, geometric means and CVs will be provided. The key secondary objectives are considered met if: 1. For FDA and PMDA requirement: CI for the ratio of the geometric mean AUEC for %CfB in serum CTX has to be completely contained within the interval [0.80, 1.25] (FDA requirement is 90% CI and PMDA requirement is 95% CI).

	To evaluate the other secondary objectives, the following data will be summarized using descriptive statistics: • BMD: %CfB of LS-BMD, FN-BMD, and TH-BMD at Weeks 26, 52, and 78 • Safety: fractures, AEs, serious AEs, related AE, AEs leading to discontinuation up to Week 78 • PD: serum CTX and PINP concentrations as per visit schedule • Serum PK parameters AUCinf and Cmax after the first dose (EMA requirement) • Denosumab serum concentrations as per visit schedule • Immunogenicity: binding and neutralizing ADAs measured up to Week 78
Key words	Denosumab, biosimilar, osteoporosis

1 Introduction

1.1 Background

Osteoporosis is defined as a progressive, systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Common sites for osteoporotic fractures are the spine, hip, distal forearm and proximal humerus (Kanis and Glüer 2000). Osteoporosis is estimated to affect 200 million women worldwide, approximately one-tenth of women aged 60, one-fifth of women aged 70, and two-fifths of women aged 80 (Johnell and Kanis 2006). It is widely recognized that osteoporosis and the consequent fractures are associated with increased morbidity and mortality.

Denosumab is a fully human monoclonal antibody that targets and binds with high affinity and specificity to Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone (Prolia EU SmPC, Prolia US PI).

GP2411 is a proposed biosimilar that is being developed by Sandoz to Amgen's denosumab (marketed as Prolia®/ marketed as Pralia® in Japan [hereafter referred to as Prolia/ Pralia] and Xgeva®/ marketed as Ranmark® in Japan [hereafter referred to as Xgeva/ Ranmark]). The development of GP2411 aims for the treatment of all indications currently approved for Prolia/ Pralia in Japan and Xgeva/ Ranmark in Japan. Biosimilarity will be supported by the totality of evidence from analytical, nonclinical, clinical pharmacokinetics (PK), pharmacodynamics (PD), efficacy, safety and immunogenicity data.

Development of biosimilar

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized biological medicinal product with demonstrated similarity in physico-chemical characteristics, biological activity, efficacy and safety, based on a comprehensive comparability exercise (Weise et al 2011; Schneider et al 2012). It is intended to be used at the same dose(s) and dosing regimen(s) to treat the same disease(s) as the reference product. The development and commercialization of biosimilars can help address unmet medical needs by improving access to well-established therapeutic interventions while improving healthcare affordability (McCamish and Woollett 2012).

Biological medicinal products are derived from living cells or organisms and consist of relatively large and complex molecular entities. Due to the inherent variability of the biological system as well as potential manufacturing process changes introduced over time, any resulting biological will display a certain range of variability, even between different batches of the same originator product (Weise et al 2011). Manufacturers and health authorities are managing this variability based on the principle that changes in quality attributes can be accepted as long as they do not alter the safety and efficacy of the biologic product (Schiestl 2011).

Development of GP2411

GP2411 (proposed biosimilar denosumab) is a genetically engineered human immunoglobulin IgG2 type monoclonal antibody directed against the transmembrane or soluble protein RANKL. The antibody has a molecular weight of 147 kDa and is composed of two heavy chains and two light chains of the kappa subclass.

Study CGP24112301 is part of the clinical development program of GP2411, and has been set up to support worldwide registration of GP2411 as a proposed biosimilar product to Amgen's denosumab (marketed as Prolia/ Pralia in Japan and Xgeva/ Ranmark in Japan). It is the first trial in which GP2411 is being administered in humans.

The study aims at using a sensitive indication and sensitive endpoints to detect any clinically meaningful differences in comparison to the comparator (EU-authorized Prolia). Accordingly, postmenopausal osteoporosis (PMO) has been selected as the indication for the study for following reasons:

- the pivotal studies on Prolia have been conducted in this indication
- patients with PMO are relatively healthy and fully immunocompetent women, thus appropriate towards detecting potential differences in the safety profile between a biosimilar denosumab and the comparator
- PMO has been recognized by the Health Authorities as representative of all indications of the originator product for conducting a biosimilar study

1.2 Purpose

The purpose of the study is to demonstrate similar PK, PD, efficacy, safety and immunogenicity of GP2411 and EU-authorized Prolia in women with postmenopausal osteoporosis. The efficacy assessment is primarily based on percent change from baseline (%CfB) in lumbar spine bone mineral density (LS-BMD) at Week 52. PD similarity will be assessed in terms of the bone resorption marker collagen C-telopeptide (CTX) after the first dose at Week 26, while PK will also be evaluated after the first dose, based on AUCinf and Cmax parameters from the PK profiles.

The study also aims at comparing the safety and immunogenicity profiles after the transition from EU-authorized Prolia to GP2411.

2 Objectives and endpoints

The study design has been discussed and agreed with FDA, EMA and PMDA. Summarized below are the various endpoints (primary, key secondary and secondary) that have been agreed with the different agencies (Table 2-1).

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate similar efficacy between GP2411 and EU-	• Percent change from baseline (%CfB) in lumbar spine BMD (LS-BMD) at Week 52 (FDA, EMA, PMDA)

Objective(s)	Endpoint(s)
authorized Prolia, in terms of BMD	
• 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 (only EMA)
• To demonstrate similar PK between GP2411 and EU-authorized Prolia	• Serum PK parameters AUCinf and Cmax after first dose (only PMDA)
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)
• **Treatment Period 1 (Day 1 − Week 52)** To compare GP2411 and EU-authorized Prolia in terms of PK, PD, efficacy, safety, and immunogenicity	• %CfB in BMD at lumbar spine, femoral neck, and total hip (LS-BMD, FN-BMD, TH-BMD) at Week 26 • %CfB in BMD: FN-BMD and TH-BMD at Week 52 • 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
• **Treatment Period 2 (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 anti-drug antibodies (ADAs) from Week 52 up to Week 78 • Denosumab serum concentrations as per visit schedule from Week 52 up to Week 78

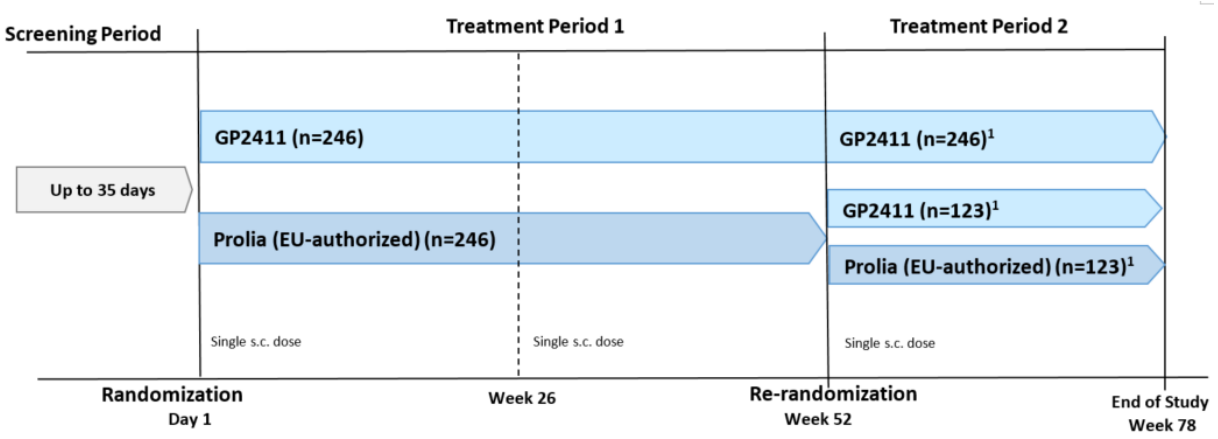
3 Study design

This is an international, multicenter, randomized, double-blind, two-arm, parallel-group study with a total duration up to 83 weeks. A total of approximately 492 women with postmenopausal osteoporosis will be randomized on Day 1 of Treatment Period 1 in a 1:1 ratio into two treatment groups. Randomization in Treatment Period 1 will be stratified by region, age group, prior bisphosphonate use and body weight group. Re-randomization in Treatment Period 2 will not be stratified.

The study consists of 3 periods: a Screening Period of up to 5 weeks to assess a patient's eligibility, a Treatment Period 1 (Day 1 to Week 52) and a Treatment Period 2 (Week 52 to Week 78).

An outline of the study periods is presented in Figure 3-1 while a detailed visit and assessment schedule can be found in Table 8-1.

Figure 3-1 Study design



[1] Number of patients could vary due to drop-outs

Screening Period (screening to randomization, Day -35 to Day 1)

The Screening Period begins once the patient has provided written informed consent to participate in the study (Visit 1) and ends at randomization visit (Visit 2) of the study. The Screening Period will be no longer than 5 weeks and will be used to assess eligibility of the patients.

Treatment Period 1 (Day 1 to Week 52)

The Treatment Period 1 begins with randomization (Day 1, Visit 2) and ends with the completion of Week 52 (Visit 15) assessments. Eligible patients will be randomized in a 1:1 ratio into one of two treatment groups, either GP2411 or EU-authorized Prolia. During the Treatment Period 1, patients should attend visits at the study site at Day 1, Day 2, Day 4, Day 8, Day 15, Weeks 8, 14, 18, 22, 26, 28, 39, 50 and 52.

The visits designated as Week 26 (Visit 11) and Week 52 (Visit 15) involve activities that belong to the end of one week and the beginning of the succeeding week. For instance, the visit

at Week 52 works as the transition between the Treatment Period 1 and the Treatment Period 2, and the assessments at this visit will serve the dual purpose of assessments for the end of Treatment Period 1, and pre-dose assessments for the Treatment Period 2 dose administration.

During the Treatment Period 1, patients will receive two doses of either GP2411 or Prolia, administered at a dose of 60 mg s.c. at Day 1 and Week 26.

Analysis of primary endpoints and secondary endpoints will be performed after all patients have completed the Treatment Period 1 (Week 52). All safety data collected for patients who have progressed beyond Week 52 will also be included in this analysis.

Treatment Period 2 (Week 52 to Week 78)

After completion of study assessments to mark the end of the Treatment Period 1, the Treatment Period 2 begins with blinded allocation of study medication through the IRT system and administration of the third dose of the study medication at the end of Week 52 (Visit 15). During this process, all patients in the Prolia group will be re-randomized 1:1 to either continue with a third dose of Prolia, or transition to GP2411. All patients in the GP2411 group will continue with a third dose of GP2411.

Analysis of Treatment Period 2 secondary endpoints will be done after all patients have completed Week 78.

4 Rationale

4.1 Rationale for study design

The study is part of the clinical development program for GP2411 and aims to support worldwide registration of GP2411 as a proposed biosimilar product to Amgen's denosumab (marketed as Prolia/ Pralia in Japan and Xgeva/ Ranmark in Japan). The concept study design has been discussed and agreed with FDA, EMA and PMDA.

The main indications of Amgen’s denosumab are the treatment of postmenopausal women at increased risk of fractures, the therapy of bone loss associated with hormone ablation in men with prostate cancer (Prolia) and the prevention of skeletal related events in adults with bone metastases from solid tumors (Xgeva). Patients with cancer treatment induced bone loss, or patients with metastatic bone disease are expected to have a larger background noise in terms of safety, due to the severity of the underlying condition, potential co-morbidities and concomitant medications. Cancer patients are also more likely not to be fully immunocompetent. The healthier and immunocompetent PMO patients are considered more sensitive to detect potential differences of adverse reactions and immunogenicity. Therefore, as also discussed in Section 1.1, Sandoz has decided to conduct this study in the appropriate and sensitive indication PMO to compare the proposed biosimilar denosumab to EU-authorized Prolia.

The study has a parallel-group design, with a total duration of 82 weeks. The primary endpoint analyses are based on data collected up to 52 weeks. As discussed in Section 3 and Section 6.1.3, the study also involves a transition from Prolia to GP2411 for 50% of the patients on Prolia, with a subsequent evaluation of PK, PD, efficacy, and particularly safety and immunogenicity up to Week 78 (26 weeks after the transition).

4.2 Rationale for dose/regimen and duration of treatment

Dose, frequency and route of administration of the study medication are chosen according to the current Prolia/ Pralia in Japan label for the therapy of postmenopausal women with osteoporosis. After the initial s.c. injection of 60 mg GP2411/Prolia on Day 1, patients will receive a subsequent 60 mg s.c. dose after 6 months (Week 26), followed by the third 60 mg s.c. dose at Week 52, at the start of the Treatment Period 2.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

GP2411 is being developed as a similar biological medicinal product to Prolia/ Pralia in Japan. EU-authorized Prolia has been chosen as the comparator in this study to confirm similarity in terms of PK, PD, efficacy, safety and immunogenicity.

4.4 Purpose and timing of interim analyses

Data analyses will be performed at two points:

- Interim analysis at Week 52: This will be carried out after all patients have completed Week 52 or discontinued prior to Week 52. In addition, the interim analysis will also include all available safety data from Treatment Period 2 which has been collected up until the partial database lock.
- Final analysis at Week 78: This will be carried out after all patients have completed the study.

The interim analysis will allow for an early read-out of primary endpoint analyses. Additional information is presented in the interim analysis Section 12.7.

4.5 Risks and benefits

Prolia has been licensed and commercialized world-wide since 2010 and Pralia in Japan since 2013. Clinical studies have provided evidence of efficacy and safety in all approved indications, including osteoporosis. In osteoporosis, it is proven to increase bone mineral density and protect bones from fracture. Since approval of Prolia/ Pralia an extensive post-marketing experience has been gathered, which confirms Prolia's/ Pralia's established safety and efficacy profile and demonstrates its favorable risk-benefit ratio (Prolia EU SmPC, Prolia US PI).

In terms of safety profile, the most common side effects for Prolia/ Pralia are back pain, pain in the arms and legs, joint and/or muscle pain and bladder infection. Uncommon or rare cases of cellulitis, hypocalcemia, hypersensitivity, osteonecrosis of the jaw and fractures of the thigh bone have been observed.

Based on the currently available analytical data, it is concluded that GP2411 and US-licensed and EU-authorized Prolia are similar at the physicochemical and functional level. Consequently, the PK, PD, efficacy, safety and immunogenicity of GP2411 in patients with postmenopausal osteoporosis are expected to be comparable to that of Prolia/ Pralia. All patients in the study will therefore be receiving active therapy with a similar expectation of benefit. The contraindications, precautions and warnings, as summarized in the Prolia EU SmPC and the Prolia US PI, will also apply to GP2411.

So far, the pandemic has not shown significant impact on trial conduct and patient compliance in terms of site visits and study procedures. As per Sandoz medical assessment, the treatment with study medication does not pose additional safety risks to the study patients in the context of the Covid-19 pandemic. Sandoz continues to carefully monitor Covid-19 related risks and implements risk mitigations as applicable according to Health Authority guidelines and internal procedures. It is the investigator's responsibility to assess local circumstances of the pandemic which might lead to a local change in the risk/benefit assessment by the investigator. In this case, this investigator driven assessment should be documented in the investigator site file and communicated to the sponsor.

4.5.1 Blood sample volume

Timings of blood sample collection are outlined in the assessment schedule Table 8-1. Additional samples may be required for safety monitoring.

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

5 Population

The study will enroll postmenopausal women with osteoporosis, with a BMD T-score ≤-2.5 and ≥-4.0 at lumbar spine measured by dual energy X-ray absorptiometry (DXA). These criteria are in accordance with the current guidelines for PMO treatment (Kanis et al 2013, Camacho et al 2016).

A total of approximately 492 patients will be randomized. Patients that drop out after they have been randomized will not be replaced.

5.1 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Postmenopausal women, diagnosed with osteoporosis.
   Postmenopausal status is defined as at least 12 consecutive months of amenorrhea prior to date of screening, for which there is no other obvious pathological or physiological cause. [For CZ only: Postmenopausal status is defined as at least 12 consecutive months of amenorrhea prior to date of screening for which there is no other obvious pathological or physiological cause and by elevated serum follicle-stimulating hormone (FSH) level assessed by central laboratory at screening]
3. Aged ≥55 and ≤80 years at screening
4. Body weight ≥50 kg and ≤90 kg at screening
5. Absolute bone mineral density consistent with T-score ≤-2.5 and ≥-4.0 at the lumbar spine as measured by DXA during the Screening Period
6. At least two vertebrae in the L1-L4 region (vertebrae to be assessed by central reading of lateral spine X-ray during the Screening Period) and at least one hip joint are evaluable by DXA

5.2 Exclusion criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study.

1. Use of other investigational drugs within 5 half-lives of the drug or until the expected pharmacodynamic effect of the drug has returned to baseline, whichever is longer, or longer if required by local regulations
2. Previous exposure to denosumab (Prolia/ Pralia in Japan, Xgeva/ Ranmark in Japan, or biosimilar denosumab)
3. History of hypersensitivity to any recombinant protein drugs or any of the excipients used in GP2411 or Prolia (excipients detailed in Table 6-1)
4. History and/or presence of one severe or more than two moderate vertebral fractures (as determined by central reading of lateral spine X-ray during the Screening Period)
5. History and/or presence of hip fracture
6. Presence of active healing fracture according to assessment of investigators
7. History and/or presence of bone metastases (see also exclusion criterion #25), bone disease, metabolic disease (except osteoporosis)that may interfere with the interpretation of the results, e.g. Paget's disease, rheumatoid arthritis, ankylosing spondylitis, osteomalacia, osteogenesis imperfecta, osteopetrosis, Cushing's disease, hyperprolactinemia or malabsorption syndrome
8. Ongoing use of any osteoporosis treatment (other than calcium and vitamin D supplements). Following rules for wash-out periods for osteoporosis treatments have to be adhered to:
    - Drugs being investigated for osteoporosis
    - Romosozumab: dose received at any time
    - Strontium or fluoride (for osteoporosis): dose received at any time
    - Intravenous bisphosphonates: dose received within 5 years prior to screening
    - Oral bisphosphonates
        - >3 years of cumulative use prior to screening
        - any dose received within 12 months prior to screening
    - Teriparatide or any PTH analogs: dose received within 12 months prior to screening
    - Tibolone, oral or transdermal estrogen, selective estrogen receptor modulators: dose received within 12 months prior to screening
    - Calcitonin: dose received within 6 months prior to screening
    - Cinacalcet: dose received within 3 months prior to screening
9. Systemic glucocorticosteroids (≥5 mg prednisone equivalent per day for ≥10 days or a total cumulative dose of ≥50 mg) within the past 3 months before screening
10. Other bone active drugs including heparin, anti-convulsives (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin releasing hormone agonists, anabolic steroids, within the past 3 months before screening
11. Oral or dental conditions:
    - osteomyelitis or history and/or presence of osteonecrosis of the jaw (ONJ)

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

12. Current uncontrolled status of hypothyroidism or hyperthyroidism
13. History and/or current hypoparathyroidism or hyperparathyroidism, irrespective of current controlled or uncontrolled status
14. Vitamin D deficiency (25 [OH] vitamin D serum level <50 nmol/L [<20 ng/mL]). An Appropriate vitamin D dose in addition to vitamin D supplementation is permitted at the investigator's discretion and patients will be retested during the screening period or may be rescreened (refer to Section 8.1)
15. Current hypocalcemia, defined as calcium <2.10 mmol/L [<8.42mg/dL] or hypercalcemia, defined as calcium >2.62 mmol/L [>10.50 mg/dL]; patients must have normal albumin values (32-55 g/L [3.2-5.5 g/dL]) according to central laboratory normal range. (Refer to Section 8.5.2 for specifications on repletion of calcium during the screening period).
16. Known intolerance to, or malabsorption of calcium or vitamin D supplements
17. History and / or presence of a severe allergic reaction (e.g. anaphylaxis)
18. History and/or presence of significant cardiac disease as per investigator's discretion, including but not restricted to:
    - ECG abnormalities at screening indicating significant risk of safety for patients participating in the study
    - history and/or presence of myocardial infarction within 6 months before screening
    - history and/or presence of NYHA class III or IV heart failure
19. Patients having at screening any of the following hematology values:
    - Hemoglobin <10.0 g/dL [<100 g/L]
    - White blood cell (WBC) count <3,500/µL [< 3.5 x 10^9 /L], or neutrophil count <2,000/µL [< 2.0 x 10^9 /L], or platelet count <125,000/µL [< 125 x 10^9 /L]
20. Renal impairment manifesting with an estimated glomerular filtration rate (eGFR) <45 ml/min
21. Cirrhosis of the liver, unstable liver disease, or elevated liver function tests to the order of ALT or AST or ALP >2 times upper limit of normal
22. Presence of clinically significant active infections (as per investigator' discretion) that may increase the risk associated with study participation
23. Positive serology indicating Hepatitis B or Hepatitis C infections
24. Positive serology for human immunodeficiency virus (HIV) infection or known diagnosis of AIDS
25. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
26. Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that

may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study

27. Known alcohol, drug or substance abuse within 12 months prior to screening
28. Patients who are legally institutionalized, or patients under judicial protection
29. Patients with an immediate family member (i.e., spouse, parent/legal guardian, sibling or a child) being a member of study site staff or being a member of the sponsor's study team

6 Treatment

6.1 Study treatment

The study medications GP2411 (proposed biosimilar denosumab) and EU-authorized Prolia will both be supplied as 1 mL pre-filled syringes containing 60 mg of denosumab (60 mg/mL).

6.1.1 Investigational and comparator drugs

Table 6-1 Investigational/ comparator drug

Name and Strength	Pharmaceutical Dosage Form	Route of Administration	Presentation
GP2411 (60 mg/mL)	Solution for injection	Subcutaneous use	Single use pre-filled syringe*
EU-authorized Prolia (60 mg/mL)	Solution for injection	Subcutaneous use	Single use pre-filled syringe

	GP2411	Prolia
Active ingredient (INN)	Denosumab	Denosumab
Concentration	60 mg/mL	60 mg/mL
Extractable volume	1 mL	1 mL
Sorbitol	4.7 %	4.7 %
Acetate	17 mM	17 mM
Polysorbate 20	0.01 %	0.01 %

* Single use pre-filled syringes are not certified (approved) in Japan

6.1.2 Additional study treatments

According to the Prolia/ Pralia label, it is important that all patients receiving denosumab must have an adequate intake of calcium and vitamin D (Prolia EU SmPC, Prolia US PI). Therefore, from screening (Visit 1) until the end of study, all patients must receive at least 1000 mg of elemental calcium and 800 IU vitamin D daily throughout the study. Compliance with calcium and vitamin D supplementation throughout the study will be monitored and assessed.

For JP only, Patients who received activated vitamin D before study start (Visit 1) have to switch to natural vitamin D.

If a patient develops hypercalcemia (calcium >2.62 mmol/L [>10.50 mg/dL]) over the course of the study, the investigator may use his/her medical judgement and reduce the calcium and/or vitamin D supplementation to maintain serum calcium concentration within the normal range. If a patient develops hypocalcemia (calcium <2.10 mmol/L [<8.42 mg/dL]) during the screening as well as over the course of the study, appropriate additional supplementation should be instituted as deemed acceptable by local guidelines, to maintain serum calcium concentration within the normal range.

The supplementation given to the patients has to be based on the regular evaluation of calcium test and serum 25-hydroxyvitamin D (25 (OH) vitamin D) levels; refer to central laboratory assessment for these two parameters in Table 8-1.

Vitamin D and calcium supplements are commercially available and are to be provided locally at the sites. The sponsor will not provide these supplies but they will be reimbursed.

For patients unable to tolerate a particular calcium or vitamin D dose or formulation, the patient should be instructed to try a different calcium or vitamin D formulation. If this approach fails and the patient remains unable to tolerate the specified dose of calcium and/or vitamin D, the investigator may document that only a lower dose is tolerated by the patient, and reduction of the supplementation dose will be allowed.

6.1.3 Treatment arms/group

At randomization (Day 1, Visit 2) patients will be randomized in a 1:1 ratio to receive either GP2411 or EU-authorized Prolia with approximately 246 patients in each arm. Randomization on Day 1 will be stratified by region, age group, prior bisphosphonate use and body weight group (see also Section 6.3.2).

Treatment Period 1 (Day 1 to Week 52)

- GP2411: s.c. administration of 60 mg of GP2411 on Day 1 and at Week 26
- Prolia: s.c. administration of 60 mg of Prolia on Day 1 and at Week 26

Treatment Period 2 (Week 52 to Week 78)

The Treatment Period 2 will begin with blinded allocation of treatment for Treatment Period 2 through the IRT system at the end of Week 52. Patients in the Treatment Period 1 Prolia arm will be randomized in a 1:1 ratio to either continue with Prolia or transition into GP2411. All patients in the GP2411 group will continue treatment with GP2411. In order to maintain the blind, the process of allocating treatment in Treatment Period 2 will be carried out for all patients in a blinded fashion through a new interaction with the IRT system. Re-randomization will not be stratified.

- GP2411: s.c. administration of 60 mg of GP2411 at Week 52
- Prolia: s.c. administration of 60 mg of Prolia at Week 52

6.1.4 Treatment duration

The planned duration of treatment is 18 months (12 months of Treatment Period 1 and 6 months of Treatment Period 2). During this period (as discussed above in Section 3) each patient will receive 3 doses of study medication at intervals of 6 months.

6.2 Other treatment(s)

No other treatments for osteoporosis other than study medication, calcium and vitamin D supplements are permitted throughout the course of the study.

6.2.1 Concomitant therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary except for those listed as prohibited medications in Section 6.2.2.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the sponsor/delegated Contract Research Organization (CRO) before randomizing a patient or allowing a new medication to be started. If the patient is already enrolled the sponsor/delegated CRO should be contacted to determine if the patient should continue participation in the study.

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions), administered after the patient was enrolled into the study, must be recorded in the appropriate electronic Case Report/Record Form (CRF). Additionally, the eCRF will also capture data on medications and procedures administered prior to study start as below:

- treatment for osteoporosis: all past treatment
- treatment not related to osteoporosis: last 3 months prior to screening

6.2.2 Prohibited medication

Use of the treatments mentioned below are prohibited during study participation (from screening up to end-of-study for an individual patient) as they are known or suspected to affect bone metabolism. In addition, as also discussed in the exclusion criteria in Section 5.2, an adequate washout period will be required for these medications prior to screening.

- Denosumab (Prolia/ Pralia in Japan, Xgeva/ Ranmark in Japan, or biosimilar denosumab)
- Investigational drugs for osteoporosis
- Romosozumab
- Strontium, fluoride (for osteoporosis)
- Intravenous bisphosphonates
- Oral bisphosphonates
- Teriparatide or any PTH analogs
- Calcitonin, oral or transdermal estrogen, selective estrogen receptor modulators
- Tibolone, cinacalcet
- Systemic glucocorticosteroids; inhaled and topical corticosteroids are acceptable
- Other bone active drugs including but not limited to heparin, anticonvulsives (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin releasing hormone agonists, anabolic steroids and vitamin K

6.2.3 Restriction for study patients

For the duration of the study, patients should be informed and reminded of the restrictions outlined in this section.

6.2.3.1 Dietary restrictions

All patients must be in fasting state prior to PD sampling. Fasting state is defined as overnight fasting; if overnight fasting is not feasible, a minimum of 8 hours fasting is required.

6.2.3.2 Other restrictions

During screening/informed consent process and scheduled visits, the patients will be informed and reminded of the following restrictions:

- avoid strenuous physical exercise the day before PD sampling
- PD samples should be taken in the morning between 7:30 and 10:00 am.

6.3 Patient numbering, treatment assignment, randomization

6.3.1 Patient numbering

Each patient is identified in the study by a unique Patient Number (Patient No.). The Patient No. consists of the Center Number (Center No.) (as assigned by the sponsor to the investigative site) and a sequential number suffixed to it, that is assigned from the Electronic Data Capture (EDC) system to the investigator when the patient is first enrolled for screening. This Patient No. is retained as the primary identifier for the patient throughout the entire participation in the trial, and with this each patient is numbered uniquely across the entire database.

In case a patient is rescreened (refer Section 8.1), the patient will need to sign a new informed consent form and a new Patient No. will be assigned by the EDC system. The date of the new informed consent signature must be entered on the appropriate eCRF under the new Patient No. Informed Consent for a rescreened patient must be obtained prior to performing any study-related assessments.

6.3.2 Treatment assignment, randomization

At the randomization (Day 1, Visit 2) all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment groups. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment group and will specify a unique medication number for the first package of study medication to be dispensed to the patient.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. In effect there will be a separate randomization list for each stratum (combination of region, age group, prior bisphosphonate use and weight group). These randomization numbers are linked to the different treatment groups, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study medication.

All patients who complete Treatment Period 1 will be allocated treatment for Treatment Period 2 at the beginning of Treatment Period 2 via IRT in a blinded fashion. Those patients in the Treatment Period 1 Prolia treatment group will be re-randomized in a 1:1 ratio to either transition to receive GP2411 in the Treatment Period 2 or continue on Prolia. Patients originally randomized to GP2411 in the Treatment Period 1 will automatically continue on GP2411 in Treatment Period 2 but this will also be performed via the IRT system to maintain the blind of treatment assignment (i.e. all patients in the GP2411 group will be re-randomized to continue on GP2411 during the Treatment Period 2).

Randomization on Day 1 for the Treatment Period 1 will be stratified by region (US, Rest of World and Japan), age group (<65 years/ ≥65 years) and prior bisphosphonates use (yes/ no) and body weight group (<70 kg/ ≥70 kg). It should be noted, however, that only a subset of the stratification factors are relevant for each of the co-primary analyses, and only the relevant factors will be included in the statistical model for each co-primary endpoint. 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.

Re-randomization at the beginning of Treatment Period 2 will not be stratified.

The randomization scheme for patients will be reviewed and approved by a member of the Novartis Randomization Office.

6.4 Treatment blinding

Patients, investigators, and the sponsor will remain blinded to study medication throughout the study, except where indicated below.

The identity of the study medications could not be concealed as the appearances of the syringes differ. To maintain the double-blind design of the study it is necessary to involve unblinded staff at the study site for handling the study medication. Unblinded site staff must not perform any clinical assessments. Prolia and GP2411 open label supply will be provided at sites to the unblinded site pharmacist. To ensure that the treatment will be blinded to the patient and the investigator, receipt, handling and administration of the s.c injection will be performed by unblinded study site personnel not involved in study assessments. All unblinded study documentation will be kept strictly confidential and will not be accessible by the blinded site staff. On a patient level, either a screen would be used to maintain blinding, or the patients will be asked to wear a blindfold during the three s.c. injections.

Unblinding will only occur in case of patient emergencies, at the time of the primary endpoint readout (only for specific sponsor personnel involved in this analysis), and at the conclusion of the study.

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study medication throughout the study.

Sponsor staff or delegate

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

- Unblinded field monitor(s)
- Unblinded clinical staff managing drug supply to site or interacting with unblinded field monitor(s)
- Unblinded designated study team members for primary endpoint readout (Week 52)
- Unblinded quality assurance and compliance clinical operation staff

The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded field monitors are not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist, and verification of used/ unused syringes.

Sponsor clinical staff are required to assist in the management and re-supply of investigational drug product. These individuals are not provided with randomization lists directly, but may be unblinded through communication of drug re-supply needs via the unblinded site pharmacists.

After all patients have completed Week 52 assessment and after the database has been partially locked for the Primary Endpoint Readout, designated study team members will be unblinded to the initial study medication assignment. Patients, investigators and the rest of the study team will remain blinded until after the final database lock. Details will be explained in a Blinding Charter.

The auditor(s) and/or sponsor quality assurance/compliance clinical operation staff, will review unblinded information during audits, compliance visits or other activities conducted by quality assurance or compliance clinical operation.

All other sponsor staff will stay blinded to treatment assignments (except in the case of a safety event necessitating unblinding) until final database lock.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure until final database lock.

Following final database lock all roles may be considered unblinded. See the blinding/ unblinding table for an overview of the blinding/ unblinding plan.

Table 6-2 Blinding and unblinding plan

Role	Time or Event Randomization list generated	Treatment allocation & dosing	Safety event (single patient unblinded)	Primary Readout Analysis
Patients	B	B	UI	B
Site staff	B	B	UI	B

Role	Time or Event Randomization list generated	Treatment allocation & dosing	Safety event (single patient unblinded)	Primary Readout Analysis
Unblinded site staff e.g. pharmacy staff, study medication administrating staff	NA	U	NA	NA
Global Clinical Supply and Randomization Office	U	U	NA	NA
Sponsor staff involved in handling of study medication, unblinded field monitoring, auditing/compliance clinical operation	NA	U	NA	NA
Sponsor staff involved in primary endpoint analysis	B	B	B	U
Pharmacovigilance sponsor staff	NA	NA	UI	NA
All other sponsor staff not identified above (trial team, project team, management & decision boards, support functions)	B	B	B	B

U: Unblinded
UI: Allowed to be unblinded on individual patient level
B: Remains blinded
NA: Not applicable to this study

6.5 Dose escalation and dose modification

Not applicable.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The information on study medication administration including any deviations will be captured in the source documents and recorded to the eCRF and will be verified by the blinded field monitor. Compliance will also be assessed by an unblinded field monitor using drug accountability information collected by IRT and counts of the pre-filled syringes.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all patients as detailed in the pharmacokinetic section (Section 8.5.2).

6.6.2 Recommended treatment of adverse events

The safety profile for Prolia/ Pralia is well established. GP2411 is a proposed biosimilar to Prolia, and hence is expected to exhibit a comparable safety profile. According to Prolia EU SmPC, the most common adverse drug reactions with Prolia are musculoskeletal pain and pain in the extremity. Uncommon cases of cellulitis, rare cases of hypocalcaemia,

hypersensitivity, osteonecrosis of the jaw and atypical femoral fractures have also been observed.

The investigators will follow local guidelines and their best medical practice and judgement to treat adverse events (AEs) accordingly. Medications used to treat AEs must be recorded on the appropriate eCRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required in order to treat the patient safely. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/ she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the study medication treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the sponsor/ delegated CRO and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide the following data to the IRT:

- protocol number
- patient number

In addition, oral and written information to the patient must be provided on how to contact the investigator's backup in cases of emergency, or when the investigator is unavailable, to ensure that un-blinding can be performed at any time.

6.7 Preparation and dispensation

Each study site will be supplied with study medication in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

Unblinded site staff will identify the study medication kits to dispense to the patient by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label). Immediately before dispensing the medication kit to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document. In addition, the medication number will be entered into the eCRF.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study medication must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only designated site personnel have access. Upon receipt, all study medication must be stored according to the instructions specified on the labels and in the Investigational Product Handling Manual. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the sponsor. Further details will be provided in the Investigational Product Handling Manual.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study medication but no information about the patient except for the medication number.

The unblinded pharmacist must maintain an accurate record of the shipment and dispensing of study medication in a drug accountability log. Monitoring of drug accountability will be performed by unblinded field monitors during site visits or remotely and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study medication, packaging, drug labels, and a copy of the completed drug accountability log to the address provided.

6.7.1.2 Handling of additional treatment

Calcium and vitamin D supplements are to be taken by patients as described in Section 6.1.2.

6.7.2 Instruction for prescribing and taking study treatment

During the 18 months of study participation (Treatment Period 1 and Treatment Period 2), patients will receive 3 s.c. doses of study medication. Each dose is one pre-filled syringe of either 60 mg GP2411 or 60 mg EU-authorized Prolia.

To reduce variability in the PK analysis, the s.c. injection will be administered only in the abdomen, by an unblinded healthcare professional at the site.

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation) IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

The sponsor will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by the sponsor before submission to the IRB/IEC.

Information about common side effects already known about the study medication can be found in the Investigator's Brochure (IB). This information will be included in the informed consent form and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient.

A copy of the approved version of all consent forms must be provided to the sponsor after IRB/IEC approval.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all assessments when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits/ assessments as outlined in the assessment schedule or as close to the designated day/ time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the Early Termination Visit will be performed. Early Termination Visit is not expected to be performed for patients not randomized or not treated.

If patients refuse to return for these assessments or are unable to do so, every effort should be made to contact them by telephone or by sending appropriate correspondence. At this contact, the safety (e.g. potential occurrence of AEs or SAEs) and the efficacy outcome as well as the primary reason for a patient's premature withdrawal should be determined.

Table 8-1 Assessment schedule

Period	Screening		Treatment Period 1												Treatment P1/ P2	Treatment Period 2			Treatment Withdrawal
Visit Name	**Visit 1 (Screening)**	**Visit 2 (Randomization)**	**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
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

Period	Screening		Treatment Period 1												Treatment P1/ P2	Treatment Period 2			Treatment Withdrawal
Visit Name	**Visit 1 (Screening)**	**Visit 2 (Randomization)**	**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**
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.

8.1 Screening

Screening

The Screening Period starts on the date the ICF is signed. Screening procedures may be performed on multiple days but must be completed within 35 days (5 weeks) prior randomization. The screening procedures are

- Informed consent
- Medical history and prior/ concomitant medication (including fracture history, active healing fracture assessment by investigators, and collecting information on bone-specific medications)
- Assessment of and instructions for calcium and vitamin D supplementation
- Physical examination
- Vital signs: blood pressure, temperature and pulse rate
- ECG
- Height and weight
- Blood samples for serum chemistry including calcium test, hematology, coagulation, and serum 25 (OH) vitamin D level as well as hepatitis and HIV screen.
  For CZ only: blood samples for serum FSH.
  For JP only: Calcium test has to be repeated at Day -4 (-3) in patients switching from activated vitamin D to natural vitamin D at Visit 1)
- Local dipstick urinalysis
- For CZ only: Urine sediment test by microscopy (conducted by the central laboratory)
- AE reporting
- Lateral spine X-ray (thoraco-lumbar) submitted to central imaging vendor as soon as possible following the visit
- DXA scan of the lumbar spine, total hip, and femoral neck to be submitted to the central imaging vendor as soon as possible following the visit

Rescreening

Rescreening will be allowed for a patient who fails to meet the serum 25 (OH) vitamin D exclusion criterion. In order to be eligible for study participation, the patient must have a serum 25 (OH) vitamin D level ≥20 ng/mL assessed by the central laboratory at rescreening.

It may be permissible to rescreen a patient if she fails the initial screening for any other reason; however, each case must be discussed and agreed with the sponsor/ delegated CRO on a case-by-case basis.

In case a patient is rescreened, the following conditions will apply:

- A new informed consent will require patient signature.
- Patient will be logged as a screen failure into the IRT and entered as a rescreen. Patient not entered into IRT as a rescreen will not be eligible for randomization.
- A new 35 day screening window will commence at this time.

- All screening procedures will be repeated; DXA not to be repeated if it is within 5 weeks of the initial scan; lateral spine X-ray not to be repeated if it is within 3 months of the initial scan.
- Patient can only be rescreened once.

8.1.1 Information to be collected on screening failures

Patients who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF as well as on the screening and enrolment log. The demographic information, informed consent, and Inclusion/ Exclusion must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a serious adverse event (SAE) during the screening phase (see SAE section for reporting details).

If the patient fails to be randomized, the IRT will be notified.

Patients who are randomized and fail to start treatment, e.g. patient randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF as well as on the screening and enrolment log.

8.2 Patient demographics/ other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: age at screening, sex, race, ethnicity, body height, body weight, relevant medical history/ current medical condition present before signing informed consent (where possible diagnoses and not symptoms will be recorded), prior/ current medications especially prior medications related to osteoporosis.

8.3 Efficacy/ Pharmacodynamics

The following parameters will be assessed to demonstrate similar efficacy and pharmacodynamics of GP2411 and Prolia:

- Change in BMD measured by DXA scan
- Change in serum bone metabolism biomarkers CTX and PINP

8.3.1 DXA scan collection, processing and analytical methods

Bone density measurements will be performed by dual-energy X-ray absorptiometry (DXA). Only bone densitometers from the manufacturers GE Healthcare (Lunar product series) and Hologic will be allowed for the study. The same DXA scanner should be used for all study procedures for a particular patient at each site. All DXA scans will be submitted to and analyzed by the central imaging vendor.

For all patients bone density will be measured at the lumbar spine, total hip and femoral neck. Lumbar spine scan must include L1 through L4 vertebrae. To be eligible for the study, patient must have at least two evaluable lumbar vertebrae (to be assessed by central reading of lateral spine X-ray during the Screening Period) and at least one evaluable hip joint.

For total hip and proximal femur, the left side should be used for all DXA scans at all study visits. If the right side must be used (e.g., due to implants) or is inadvertently used at baseline, then it must be used consistently throughout the study.

Detailed instruction for DXA scan acquisition can be found in the separate Imaging Manual.

BMD Assessments

DXA scan will be used to determine changes in BMD. DXA scan data will be submitted electronically to the central imaging vendor for analysis. Sites unable to submit data electronically can submit on CD as specified in the Imaging Manual, but electronic submission is preferred. The results from the central imaging vendor will be used as the final data for statistical analysis.

After analysis by the central imaging vendor, a study site may be asked to re-acquire a scan due to malpositioning or other technical reasons. The study sites should comply with the requests from the central imaging vendor.

8.3.2 Bone metabolism biomarkers

The effect of GP2411 and Prolia on the bone metabolism markers CTX (bone resorption) and PINP (bone formation) will be assessed in serum. CTX is a break-down product and PINP a by-product in the deposition of collagen I, the principal constituent of bone. PINP and CTX have been recommended by the International Osteoporosis Foundation and the International Federation of Clinical Chemistry Bone Marker Standards Working Group as reference markers of bone turnover for fracture risk prediction and monitoring of osteoporosis treatment (Eastell and Szulc 2017).

8.3.2.1 Biomarker blood sample collection and processing

PD samples will be collected at the visits defined in the assessment schedule Table 8-1. All blood samples for the CTX and PINP assessment should be collected at the same time of day, between 7:30 am and 10 am and must be obtained from patients in the fasting state as indicated in Section 6.2.3.1 and Section 6.2.3.2. The actual sample collection date and time must be recorded on the appropriate eCRF. Blood samples of approximately 5 mL will be collected at each sampling time point by either direct venipuncture or an indwelling cannula inserted in a forearm. A total of 12 blood samples will be collected per patient for PD assessment. The instruction regarding sample collection, numbering, processing, storage and shipment are outlined in the Laboratory Manual.

The study serum samples will be stored in freezers (-70°C) in an access controlled area for up to 15 years.

8.3.2.2 Analytical methods for quantification of bone metabolism biomarkers

CTX and PINP serum concentrations will be determined by a validated ligand-binding immunoassay. Concentrations will be expressed in mass per volume units. Measurements will be performed at the Sponsor's bioanalytical laboratory.

8.3.3 Appropriateness of efficacy assessments

Published literature shows that efficacy based on fracture prevention alone is not sensitive enough to detect small but potentially clinically meaningful differences (Kanis et al 2003). FDA has recognized that in certain cases, PD markers may be more appropriate than clinical efficacy parameters, to demonstrate that there are no clinically meaningful differences between a proposed biosimilar and the reference product (CDER 2015). BMD has been demonstrated to correlate with vertebral fracture risk reduction with denosumab treatment and its applicability as surrogate marker of risk for fractures has been demonstrated for a multitude of treatments for osteoporosis with long duration of follow-up. However, CTX, although it lacks large evidence as surrogate marker of fracture risk reduction, has the highest dynamic range of bone metabolism biomarkers and seems to be the most sensitive PD endpoint to detect potential differences between GP2411 and the comparator. BMD has a very low dynamic range and very high inter-patient variability making it a less sensitive marker. Thus, CTX (better dynamic response) and BMD (greater clinical relevance) are both considered of importance and should meet clearly justified and pre-specified equivalence criteria, based both on clinical and statistical arguments. Assessment of the bone formation marker PINP in the study allows for further evaluation of similarity of efficacy of the biosimilar compared to the comparator.

8.4 Pharmacokinetics

The following pharmacokinetic parameters will be determined from the serum concentration-time data using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher): Cmax and AUCinf after the first dose.

8.4.1 Pharmacokinetics blood sample collection and handling

Denosumab serum concentrations will be measured throughout the trial as indicated in the Assessment schedule in Table 8-1. In case a patient will not be able to attend the site at the scheduled time and date, allowed time windows are also described in the assessment schedule. The actual sample collection date and time will be recorded in the eCRF. For each sample approximately 5 mL blood will be drawn at each sampling time point by either direct venipuncture or an indwelling cannula inserted in a forearm. A total of 14 blood samples will be collected per patient for PK assessment. Blood samples will be taken, numbered, processed to serum and shipped and stored according to instructions provided in the Laboratory Manual.

The study serum samples will be stored in freezers (-70°C) in an access controlled area for up to 15 years.

8.4.2 Analytical methods for pharmacokinetics

The analytical method to be used for PK analysis related to this study will be a ligand binding assay. Briefly, the concentration of free denosumab will be determined by binding to coated ligand molecules. Concentrations will be expressed in ng/mL. All PK assessments will be performed at the Sponsor's bioanalytical laboratory.

8.4.3 Appropriateness of pharmacokinetic measurements

The PK assessments in all patients randomized in this trial are recognized as appropriate tools to assess pharmacokinetics between the drugs tested in the study. PMO women are fully immunocompetent, which allows a reliable assessment of PK parameters. The PK sampling time points are set to characterize and to capture potential differences in PK between GP2411 and EU-Prolia.

8.5 Safety

Safety assessment will consist of monitoring and recording all AEs and SAEs, the regular monitoring of hematology, blood chemistry, regular measurement of vital signs and physical examinations. The randomization and first administration of study medication will be performed on the basis of safety assessments obtained from the screening period. Safety laboratory assessments taken on Day1, Day 155 (±3), Day 366 (±3) and end of study visit will help safeguard patients throughout trial conduct. Safety laboratory assessments on Day 1 are taken to determine patients' status quo prior to the start of study treatment. For calcium assessment, refer to hypocalcemia section below for the detail of calcium evaluation before each drug administration.

Safety assessments are specified below with the assessment schedule (Table 8-1) detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 10.1.1.

8.5.1 Physical examination and vital signs

Physical examination	A complete physical examination, including general appearance, skin (presence of rash), neck (including thyroid), eyes, ears, nose, throat , lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological examination will be performed at Screening, Week 52 and End of Study Visits. At all other visits, a short physical examination including the examination of general appearance will be done, unless a complete physical examination is required (at the investigator's discretion). If possible, assessments for an individual patient should be performed by the same member of the study site staff throughout the study. Information for all physical examinations will be recorded in the source documentation at the study site only. Actual results of the physical examination will only be recorded in the eCRF if any clinically relevant finding is observed. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the eCRF. Significant findings made after first administration of study medication which meet the definition of an AE must be recorded on the AE section of the eCRF.
Vital signs	Vital signs (including body temperature, blood pressure and pulse rates) will be assessed as indicated in Table 8-1.

	After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured twice using a validated device, with an appropriately sized cuff. The two measurements should be entered in the eCRF and the average of the two measurements will be used for analysis. When the timing of these measurements coincides with blood collection, the blood pressure and pulse rate should be obtained first. For visits with study dosing, vital signs should be taken prior to study medication administration.
Height and weight	Height and body weight will be measured as listed in Table 8-1. Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing but without shoes).

8.5.2 Laboratory evaluations

A central laboratory will be used for analysis of all specimen [screening as well as on-study evaluations for serum chemistry including calcium test, hematology, coagulation, serum 25 (OH) vitamin D tests and serology test, for CZ: serum FSH] listed below in Table 8-2. [redacted]

All blood samples will be obtained by venipuncture, at the time points outlined in the assessment schedule in Table 8-1. The date and time of blood collection will be recorded in the patient's medical record.

Unscheduled laboratory assessments may be obtained at any time during the study to assess any perceived safety concerns.

The investigator will evaluate the clinical relevance of each laboratory value outside of the reference range. This evaluation will be based upon the nature and degree of the observed abnormality. Values considered clinically relevant will be identified on the clinical laboratory report and an AE will be documented in the eCRF. Additionally, abnormal laboratory values that induce clinical signs or symptoms or that require therapy must also be recorded as AEs in the eCRF. In case of an abnormal result, the investigator may consider to repeat the test once in order to rule out laboratory error.

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

Table 8-2 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 (equals Total calcium), Albumin adjusted serum calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Total Bilirubin, Blood Urea Nitrogen (BUN), Glucose

Test category	Test Name
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
Additional tests	Serum 25 (OH) vitamin D level
COVID-19 related testing	serological test for antibodies against SARS-CoV-2
For CZ only: FSH	Serum FSH level

Hypocalcemia

Hypocalcemia (calcium <2.10 mmol/L [<8.42 mg/dL]) must be corrected by adequate supplementation of calcium and vitamin D before initiating treatment and each administration of study medication.

During the screening period, if patient calcium level is >2.0 mmol/ [>8.02 mg/dL] and <2.10 mmol/L [<8.42 mg/dL], calcium repletion is permitted only for the patients who had no calcium supplementation at all or a previous calcium supplementation of <1000 mg. In these patients, calcium re-test during the screening can be performed or patient may be re-screened. Patients with a calcium supplementation of ≥ 1000 mg per day before the screening visit and/or with calcium values <2.0 mmol/L [<8.02 mg/dL] are not allowed to enter into the study. Repletion should be conducted according to the local guideline or standard of care.

Clinical monitoring of calcium level and vitamin D will be performed as indicated in Table 8-1. Since the calcium level needs to be known prior to the administration of study medication, the measurement from the following time points would be used:

- 1st dose at Day 1: calcium level from screening
- 2nd dose at Week 26: calcium level from Week 22
- 3rd dose at Week 52: calcium from Week 50

Local dipstick urinalysis

Dipsticks will be provided by the central laboratory to the sites for local urinalysis assessments. The sites will record the results in the appropriate eCRF page for each patient. Dipstick measurements for ketones, pH, protein, glucose, and blood will be done at scheduled visits as indicated in Table 8-1.

Urine sediment test (for CZ only)

In addition to the urine dipstick, a microscopic urine sediment test will be performed at the central laboratory, and will be done at scheduled visits as indicated in Table 8-1 for the analysis of potentially existing red blood cells, white blood cells, epithelial cells, bacteria, casts and crystals in the urine. The sites will record the results in the appropriate eCRF page for each patient. Any abnormal finding that is deemed clinically significant must have a corresponding adverse event reported in the applicable page in eCRF.

8.5.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity and the emergence of antibodies to human recombinant proteins is well documented. Antibodies directed against a therapeutic agent may have neutralizing activity and interfere with the efficacy of the treatment. For safety reasons, evaluation for anti-drug antibodies (ADA) has been included in this study.

Data specific to denosumab from Amgen revealed a low incidence of immunogenicity, with less than 1% of patients exposed to the medication in clinical studies developing ADAs. The immunogenicity risk of the product is considered low.

8.5.3.1 Immunogenicity blood sample collection and handling

Immunogenicity will be assessed by measuring anti-drug antibody (ADA) levels in serum of all patients. Blood samples will be collected at the time points indicated in the assessment schedule Table 8-1 from all patients randomized and treated, in order to detect antibody formation against denosumab.

Blood samples of approximately 8 mL will be collected at each sample time point by either direct venipuncture or an indwelling cannula inserted in a forearm. A total of 12 blood samples will be collected per patient for immunogenicity assessment.

Serum will be prepared from blood and each sample will be labeled at the investigator's site as per the instructions in the Laboratory Manual. The actual sample collection date and time will be entered on the appropriate eCRF.

Complete instructions for sampling, processing, handling, shipment and storage will be provided in the Laboratory Manual.

The study serum samples will be stored in freezers (-70°C) in an access controlled area for up to 15 years.

Communication of immunogenicity results to investigators occurs after data base lock and finalization of the Clinical Study Report.

8.5.3.2 Analytical methods for immunogenicity determination

Immunogenicity of denosumab will be determined by the formation of antibodies against the drug and will be evaluated by using validated immunoassays.

All samples will first be analyzed in a screening assay. Study samples with a result below the validated screening cut-point are negative for binding anti-drug antibodies and will be reported accordingly. In the event of a positive result (result above or equal to the screening cut-point), the sample will additionally be analyzed in a secondary confirmatory assay (specificity assay). In case the assay signal can be reduced after addition of excess of denosumab beyond or equal to the validated confirmatory cut-point, a sample will be reported as confirmed positive for binding anti-drug antibodies. In contrast, samples with a result above the screening cut-point in the screening assay but which are negative in the confirmatory assay will be reported as negative.

The titer of confirmed positive results will be determined. In addition, samples which were confirmed to be positive for binding anti-denosumab antibodies may be analyzed for their

neutralization potential in a neutralizing antibody (NAb) assay. All immunogenicity assays will be performed at the sponsor's bioanalytical laboratory.

8.5.4 Fractures

As a safety measure, fracture rates (incidence of vertebral fractures and nonvertebral fractures) will be captured throughout the period of the study.

Vertebral fracture

Information on vertebral fractures will be centrally evaluated through the scheduled lateral thoraco-lumbar spine X-ray as indicated in the assessment schedule Table 8-1. Procedural instructions on X-rays will be provided in the Imaging Manual.

For central assessment of vertebral fractures by lateral spine X-ray, a visual semiquantitative grading scale will be used (Genant et al 1993). Details on the grading scale are provided in the Imaging Manual.

Nonvertebral fractures

Information about any nonvertebral fractures while on study will be recorded as AE. The diagnosis of nonvertebral fractures will not require central X-ray reading and will be based on local radiology reports.

8.5.5 Injection site reactions

The injection site reaction assessment will be done by the investigator/ designee. It consists of grading the severity of each injection reaction based on criteria (CTCAE) mentioned below in Table 8-3. Injection site reactions with a grading ≥1 will also be recorded as AE.

Table 8-3 Injection site reaction grading

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

8.5.6 Electrocardiogram (ECG)

According to Prolia/ Pralia label, rarely, patients receiving Prolia/ Pralia may develop hypocalcemia, which may also lead to QT prolongation.

A standard 12-lead ECG will be performed at time points as indicated in Table 8-1.

ECGs should be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs and blood sampling. The Fridenricia QT correction formula (QTcF) should be used for clinical decisions.

If the ECG findings at screening are clinically significant and would prevent the patient from participating in the study (taking into account the patient's overall status as well as the treatment profile), the patient should not be randomized into the study.

Throughout the course of the study, in the event that a clinically significant ECG abnormality is identified (e.g. severe arrhythmia, conduction abnormality of QTcF >500 ms), two more ECGs will be repeated to confirm the diagnosis, with the diagnosis decision based on the presence of the abnormality in at least two of the three ECGs.

Clinically significant abnormality must be recorded on the eCRF as either medical history/ current medical conditions or AEs as appropriate.

8.5.7 Pregnancy and assessments of fertility

For the post-menopausal women population in the study, pregnancy is not expected. However, for exceptional rare occurrence of pregnancy, the process must be followed as described in Section 10.1.4.

8.5.8 Appropriateness of safety measurements

The safety assessments being used in this study are standard for osteoporosis indication, and also aligned with the safety assessments required as per the safety profiles for EU-authorized, US-licensed Prolia and JP-licensed Pralia (Prolia EU SmPC, Prolia US PI).

8.6 Additional assessments

8.6.1 Clinical outcome assessments (COAs)

Trial feedback

This trial will include a "Trial Feedback Questionnaire", an option for patients to complete an anonymized questionnaire to provide feedback to the sponsor on their clinical trial experience. Individual patient level responses will not be reviewed by investigators. Responses would be used by the sponsor to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the patient's disease, symptoms, treatment effect or AEs and therefore would not be trial data.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study medication for a patient occurs when study medication is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

Reasons for discontinuation from study medication may include, but will not be limited to:

- Patient decision
- Pregnancy

- AEs that in the judgment of the investigator, taking into account the patient's overall status, prevent the patient from continuing the study medication or study (for example osteonecrosis of the jaw).
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevent the patient from continuing participation in the study.
- Unsatisfactory therapeutic effect
- Any situation, in which study participation might result in a significant risk to the patient's safety
- Following emergency unblinding

If discontinuation of study medication occurs, the investigator should make effort to understand the primary reason for the patient's premature discontinuation of study medication and record this information.

Patients who discontinue study medication should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdrawal of informed consent Section 9.1.2). **Where possible, they should return for the assessments indicated** in the assessment schedule, up to the next scheduled study medication administration visit (this next dose would not be administered to such a patient). The last of such scheduled visits should act as the early termination visit for the patient. If they fail to return for these assessments (post discontinuation of study medication) for unknown reasons, every effort (e.g. telephone, e-mail, or letter) should be made to contact the patient/ pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

After study medication discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/ email contact:

- new/ concomitant treatments
- AEs/ SAEs

The investigator is advised to provide appropriate follow-up antiresorptive osteoporosis treatment for all patients discontinued from the study, especially for those with high risk of fractures.

The investigator must also contact the IRT to register the patient's discontinuation from study medication.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.2 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/ her consent and record this information.

Study medication must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed, unless safety findings require communicating or follow-up and upon agreement of the patient, an early termination visit as per Table 8-1 will be conducted.

The sponsor will continue to retain and use all research results (data) that have been collected for the study evaluation.

9.1.3 Early termination visit

Patients who prematurely withdraw consent towards study participation for any reasons during the Treatment Period 1 or Treatment Period 2 should be asked to undergo the assessments as per Early Termination Visit in Table 8-1. For the definition of withdrawal of consent, please refer to Section 9.1.2.

9.1.4 Lost to follow-up

For patients, whose status is unclear, because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed.

9.1.5 Early study termination by the sponsor

The study can be terminated by the sponsor under certain circumstances.

Examples of reasons for early termination but not limited to:

- unexpected, significant, or unacceptable safety risk to patients enrolled in the study
- decision based on recommendations from applicable board(s) after review of safety and efficacy data
- discontinuation of investigational drug development

In taking the decision to terminate, the sponsor will always consider the patient welfare and safety. Should early study termination be necessary, patients must be seen as soon as possible (instructions would be provided for contacting the patient, when the patient should stop taking drug, when the patient should come for a final visit) and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure, that adequate consideration is given to the protection of the patient's interests. The investigator or sponsor, depending on the local regulation, will be responsible for informing IRBs/ IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as the date when the last patient finishes the End of Study Visit/ Early Termination Visit, or the date at which the last data point from the last patient is received, whichever is later.

The investigator is advised to provide appropriate follow-up antiresorptive osteoporosis treatment for all patients completed the study, especially for those with high risk of fractures.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual patient and identifying AEs.

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings or other assessments.

AEs must be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The Common Terminology Criteria for Adverse Events (CTCAE) grade. AEs will be assessed and graded according to the CTCAE version 5.0 or higher. If CTCAE grading does not exist for an AE, the severity of such AE should be graded as follows:
    - Grade 1: asymptomatic or mild symptoms; clinical or diagnostic observations only
    - Grade 2: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
    - Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living
    - Grade 4: Life-threatening consequences; urgent intervention indicated
    - Grade 5: Death related to AE

2. its relationship to the study medication. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/ or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient.
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/ not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study medication

All AEs must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Drug withdrawn

6. its outcome
    a. not recovered/ not resolved;
    b. recovered/ resolved;
    c. recovering/ resolving,
    d. recovered/ resolved with sequelae;
    e. fatal; or unknown

Conditions that were already present at the time of informed consent should be recorded in medical history of the patient.

AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

AE monitoring should be continued until the End of Study Visit for a particular patient. For patients that have withdrawn consent or discontinued treatment, please refer to Section 9.1.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from

baseline or the previous visit, or values, which are considered to be non-typical in patients with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any AE [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (ICH E15A 1993).

- results in persistent or significant disability/ incapacity
- constitutes a congenital anomaly/ birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (bone fragility and increased risk of fractures) .
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (ICH E15A 1993).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious AE, irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring from the time of informed consent until the patient's last study visit must be reported to sponsor safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study medication, a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. *Sponsor* may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study medication that this SAE has been reported.

All potential risks, including Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with expectations set forth in national regulatory requirements of participating countries (including, but not limited to EU Guidance 2011/C 172/01 (EUR-Lex 2011/C 172/01) and 15 CFR 312.32 (c) in the US)

Any SAEs experienced after the last study visit for each patient should only be reported to the sponsor Safety if the investigator suspects a causal relationship to study medication.

10.1.4 Pregnancy reporting

Pregnancies

For the post-menopausal women population in the study, pregnancy is not expected. However, for exceptional rare occurrence, the following process must be followed.

As a general rule, the study medication must be discontinued, though the patient may stay in the study and follow the assessments, if she wishes to do so. Each pregnancy occurring after signing the informed consent must be reported to the sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/ or newborn complications.

Pregnancy should be recorded and reported by the investigator to the sponsor CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study medication any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/ abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study medication errors and uses outside of what is foreseen in the protocol will be recorded on appropriate eCRF, irrespective of whether or not associated with an AE/ SAE, and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/ SAE within 24 hours of investigator's awareness.

Table 10-1 Guidance for capturing the study medication errors including misuse/ abuse

Treatment error type	Document in Dose Administration eCRF (Yes/ No)	Document in AE eCRF	Complete SAE form
Unintentional study medication error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/ Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional safety monitoring

Not applicable.

11 Data collection and database management

11.1 Data collection

All data captured for this study will have an external originating source (either written or electronic) with the eCRF not being considered as source.

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/ or verification of the entered data by the investigator staff.

The investigator/ designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the patient data for archiving at the study site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Sponsor personnel (or designated CRO) will review the data entered by site's staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the study site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant and prior treatment, entered into the database, will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/ current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes and data about all study medication(s) dispensed to the patient and all dose changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to the sponsor (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and field monitor. The code break functionality will remain available until study shut down or upon request of the sponsor.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by the sponsor.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator meeting, a sponsor and/ or delegated CRO representative will review the protocol and data capture requirements (i.e. eSource or eCRFs) with the investigators and their staff. During the study, the sponsor employs several methods of ensuring protocol and GCP compliance and the quality/ integrity of the sites' data. Blinded and unblinded field monitor will visit the site to check the completeness of patient records, the accuracy of data capture/ data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study medication is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the blinded and unblinded field monitor, respectively, during these visits. Remote monitoring of each site's data will be performed by the delegated CRO. Additionally, the delegated CRO will analyze data centrally and identify risks and trends for site operational parameters, and provide reports to the sponsor clinical teams to assist with trial oversight. Details on blinded and unblinded monitoring activities as well as on centralized monitoring are described in the study specific Monitoring Plan. The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or

clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the field monitor access to all source documents to confirm their consistency with the data capture and/ or data entry. The sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/ exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

To support the investigators and their staff with retention and the prevention of missing data, ongoing training will be provided by the field monitor during monitoring visits. A Visit Reminder Messaging Service implemented as an option has also been made available for those sites that do not have a visit reminder procedure in place for their patients. Investigators will additionally have the option to arrange transportation services or receive transportation reimbursement for patients who require assistance with travel to their study visits.

12 Data analysis and statistical methods

Data analysis will be performed at two time points: an interim analysis after all patients completed Treatment Period 1 and a final analysis after all patients completed the study.

The interim analysis will include the primary endpoint analysis and will compare GP2411 with Prolia for Treatment Period 1 with a 1:1 ratio. Final analysis will be completed including the data collected from Week 52 until the end of the study at Week 78 comparing the three groups "Continued GP2411", "Continued Prolia" and "transition into GP2411" and will be descriptive only. The number of patients in the three groups in Treatment Period 2 are expected to be in the approximate ratio 2:1:1 respectively.

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

Table 12-1 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 [-2.00%, 2.00%]	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

Health Authority	Endpoint	Equivalence criteria	Analysis set
	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 12-2 List of secondary endpoints with equivalence testing

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

Endpoints will be described in the primary endpoint section when the endpoint is primary for any health authority and will be referenced in the secondary endpoint sections as necessary. Of note, the testing requirement for LS-BMD is different for different HAs and therefore a situation may arise where criteria for some HA are met while for other HAs they are not. Testing strategy is detailed in Section 12.5.2.

Data collected during the study conduct can be used for submission to health authorities, ethic committees or IRBs. Any data analysis carried out independently by the investigator should be submitted to Sandoz/Hexal before publication or presentation.

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 as well as serum drug, CTX and PINP concentrations, the CV% mean, geometric mean and geometric coefficient of variation (%) (CV% geometric mean) will also be presented.

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.

12.1 Analysis sets

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

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

The **Treatment Period 1 Full Analysis Set (TP1 FAS)** is a subset of 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 at Week 52 or at both visits) is available. Patients will be analyzed according to the treatment randomized to.

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 treatment received.

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 patients received treatment according to protocol at Day 1 and Week 26
- They experienced no relevant protocol deviations which would affect LS-BMD up to Week 52 (the time of the primary analyses)

The **PD Analysis Set (PDS)** is a subset of the 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 (further details will be provided in the statistical analysis plan (SAP))
- The patients received treatment according to protocol at Day 1
- They experienced no relevant protocol deviations which would affect CTX measurements up to Week 26 (the time of the primary analyses)

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 or AUCinf) is evaluable
- The patients received treatment according to protocol at Day 1
- They experienced no relevant protocol deviations affecting the PK parameters up to Week 26 (the time of the primary analyses)

Separate PK analysis subsets may be defined for different PK parameters if deemed necessary. This will be described in detail in the SAP.

The criteria to qualify a protocol deviation as leading to exclusion from PPS, PDS or PKS will be documented in the SAP version finalized before database lock.

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.

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.

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

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. If analyses sets comprise the same patients only one may be used for analysis.

12.2 Patient demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will summarized descriptively in TP1 for the TP1 SAF, TP1 FAS, PPS, PDS and PKS and in TP2 for the TP2 FAS and TP2 SAF.

Descriptive statistics will be produced for age as a continuous variable, but age will also be included as age group (<65 years/ ≥65 years), and body weight as a continuous variable and body weight group (<70 kg/ ≥70 kg)

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, for all patients in TP1 for the TP1 SAF and in TP2 for TP2 SAF.

12.3 Treatments

Study medication administration will be summarized for the respective safety set.

Number of doses will be summarized as frequency and percentage including duration of exposure.

Concomitant medications and significant non-drug therapies after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system for both safety sets. In addition, osteoporosis treatment prior to the start of study treatment will be summarized similarly.

12.4 Pharmacokinetics and pharmacodynamics

12.4.1 Pharmacokinetics

Serum samples will be analyzed for free denosumab serum concentrations. PK parameters following the first 60 mg s.c. dose of study medication will be estimated using non-compartmental analysis (best-fit method) with Phoenix WinNonlin (Version 8.0 or above) by the pharmacokineticist of a CRO. The main PK parameters, together with the abbreviations and definitions are provided in Table 12-3. More details regarding additional PK parameters and how they are calculated will be outlined in the SAP.

Table 12-3 Pharmacokinetic parameters

Parameter	Description
AUCinf	The area under the serum concentration-time curve measured from the time of dosing and extrapolated to infinity [ng x day/mL]
Cmax	The maximum observed serum concentration [ng/mL]

12.4.2 Pharmacodynamics

Serum samples will be analyzed for CTX and PINP concentrations. PD parameters of CTX only following the first s.c. dose of 60 mg study medication will be estimated using the non-compartmental drug effect model in Phoenix WinNonlin (Version 8.0 or above) by the Pharmacokineticist of a CRO. The area under the effect versus time curve (AUEC) of baseline corrected serum CTX concentrations (% change from baseline) will be the main parameter of interest. The AUEC will be calculated as the area under 0 after the first 60 mg s.c. dose 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 up to 26 weeks will be calculated. In addition, the rebound area, where applicable, will be calculated following the first 60 mg s.c. dose. The PD parameters together with the abbreviations and definitions are provided in Table 12-4.

More details regarding the definition of different CTX areas and how they are calculated will be outlined in the SAP.

Table 12-4 Pharmacodynamic parameters

Parameter	Description
AUEC	The area that is below 0 and above the response curve [% x day]
Rebound area	The area that is above 0 and below the response curve [% x day]

12.5 Analysis of the primary endpoint(s)

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 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.

12.5.1 Definition of primary endpoint(s)

A list of primary endpoints with respective primary analysis sets applicable to different health authorities is provided in Table 12-1.

For LS-BMD and CTX the %CfB is defined as

$$\%CfB = 100 * \frac{PostBaseline - Baseline}{Baseline}$$

where PostBaseline is the the post-baseline LS-BMD or CTX value and Baseline is the baseline LS-BMD or CTX value.

Definitions of AUEC, Cmax and AUCinf and can be found in Section 12.4.

12.5.2 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 12-5, testing strategy for EMA in Table 12-6 and testing strategy for PMDA in Table 12-7 and results will be presented in one clinical study report.

Table 12-5 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

Table 12-6 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 [-2.00%, 2.00%]	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 12-7 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

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

12.5.2.1 %CfB in LS-BMD

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 for EMA and PMDA requirements will be concluded if the 95% CI for the difference in mean changes is contained within the interval [−2.00%, 2.00%], and for FDA requirement if the 95% CI of the difference is contained within the interval [-1.45%, 1.45%].

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

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

The primary analysis will be based on the least-squares mean treatment differences at Week 52 (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].

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. In case some strata are not sufficiently large enough to ensure appropriate analysis inclusion of strata into the primary analysis model may be revised in the SAP.

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 12-1). The respective analysis set will be used as supplementary analysis (see Section 12.5.5). For handling of missing data see Section 12.5.3.1.

12.5.2.2 AUEC after the first dose for CTX

The assessment of bioequivalence will be based upon the CIs (95% for EMA) of the ratio of the geometric means (test/ reference) 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 [0.80, 1.25].

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

$$H_0: \mu_{CTX,T}/\mu_{CTX,R} \leq 0.80 \; or: \; \mu_{CTX,T}/\mu_{CTX,R} \geq 1.25$$

versus

$$H_1: 0.80 < \mu_{CTX,T}/\mu_{CTX,R} < 1.25$$

ANCOVA will be performed on the log-transformed AUEC.

The ANCOVA model will include the following variables

- treatment as fixed effect
- 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 bioequivalence at the 2.5% significance level (Schuirmann 1987), 95% CIs for the ratio will respectively be derived for AUEC.

Stratification factors age, prior bisphosphonate use, weight and region were implemented for other reasons than impact on AUEC of %CfB in CTX (see Section 12.5.2.1) and therefore are not included in the model.

The primary analysis will be based on the PDS.

Descriptive statistics of AUEC of %CfB in serum CTX concentrations after the first dose will be presented by treatment group.

12.5.2.3 PK parameters after the first dose

The assessment of bioequivalence 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 [0.80, 1.25].

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

$$H_0: \mu_{PK,T}/\mu_{PK,R} \leq 0.80 \; or: \; \mu_{PK,T}/\mu_{PK,R} \geq 1.25$$

versus

$$H_1: 0.80 < \mu_{PK,T}/\mu_{PK,R} < 1.25$$

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

- treatment as 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.

Stratification factors age, prior bisphosphonate use and region were implemented for other reasons than impact on PK parameters (see Section 12.5.2.1) and therefore are not included in the model.

The primary analysis will be based on the PKS.

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

12.5.3 Handling of missing values/discontinuations

For the primary endpoints of %CfB in LS-BMD until Week 52 patterns of missing data will be observed and summarized by reason and treatment group.

12.5.3.1 %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 12.5.2.1 if the Week 26 or Week 52 LS-BMD (if applicable) 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 12-8 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 is expected to be performed at site and missing a dose would lead to patient discontinuing study 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 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 12.5.4.

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.

Any LS-BMD values measured outside of the visit window will still be considered in the analysis, however, the patient may be excluded from the PPS because of visit window violations. The visit windows leading to exclusion from the analysis sets will be documented in the SAP version finalized before database lock.

12.5.3.2 AUEC after the first dose for CTX

The AUEC of %CfB in serum CTX will be calculated if the baseline (pre-treatment) CTX value and the CTX values at Visit 4, Visit 9 and Visit 11 are available. Otherwise, the AUEC will be missing and the patient will be excluded from this primary analysis.

Serum CTX concentrations below LLOQ will be treated as LLOQ for the AUEC calculations.

12.5.3.3 PK parameters after the first dose

For PK parameter calculations below LLOQ values will be treated as missing, except for the pre-dose sample, which will be treated as zero.

12.5.4 Sensitivity analyses

Sensitivity analysis to assess robustness of normality assumption for 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. fail a Shapiro-Wilks test at p=0.05 level) then a 95% non-parametric Hodges-Lehmann CI for the difference between the treatment groups will also be calculated on the subset of patients with a Week 52 %CfB in LS-BMD value available. This will be done in order to assess the sensitivity of the results to a possible departure from the normality assumption underlying the MMRM.

Sensitivity analysis to assess robustness of MAR assumption for MMRM performed on the TP1 FAS

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 12.5.3.1).

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 -2.00%. Missing values directly related to COVID-19 pandemic will still be considered MAR. This analysis is to explore the potential impact of different assumptions about the missing data patterns.

The MI method for missing data in this analysis will be based on the algorithm proposed by Carpenter et al 2013. To build the joint distribution of pre- (Week 26) and postdeviation (Week 52) data, a proposal by Koch 2008 adapted to the biosimilar setting will be followed. In order to avoid bias in the direction of making arms more similar and thereby possibly increasing the likelihood of an incorrect demonstration of equivalence, as a second step all imputed values separately for the biosimilar arm and reference arm are made worse by the margin δ for LS-BMD for which larger positive values represent better response. Hereby, the first step will remain the same, but there will be two different scenarios for the second step.

- Step 1: get an estimate for the Week 52 missing data in both arms by deriving the patient's pre-deviation distribution per the algorithm specified by Carpenter assuming MAR
- Step 2 (derive the patient's joint distribution of pre- and postdeviation data by reducing the mean Week 52 value by δ):

a. Reduce the mean Week 52 value for the biosimilar arm (but not the reference arm) by the margin δ of 1.45%
b. Reduce the mean Week 52 value for the reference arm (but not the biosimilar arm) by the margin δ of 1.45%

This analysis will also be performed for 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.

More details of this sensitivity analysis will be provided in the SAP.

[redacted]

12.5.5 Supplementary analyses

For LS-BMD primary analysis from both PPS and TP1 FAS the analysis set that is not considered primary will be used as supplementary analysis using the methodology as specified for the primary analysis for the respective other analysis set in Section 12.5.2.1. Supportive analyses

Descriptive analysis of the rebound area will be conducted to demonstrate robustness of the co-primary CTX AUEC endpoint. More details regarding the supportive analysis and the definition of the area will be outlined in the SAP.

12.6 Analysis of secondary endpoints

12.6.1 Efficacy endpoints

For Treatment Period 1 (Day 1 to Week 52) LS-BMD, FN-BMD, TH-BMD values and associated %CfB will be summarized descriptively by treatment at the completion of Weeks 26 and Week 52. This will be performed for the PPS and TP1 FAS.

For Treatment Period 2 (Week 52 to Week 78) LS-BMD, FN-BMD, TH-BMD values (%CfB) will be summarized descriptively by treatment group. This will be performed for the TP2 FAS.

12.6.2 Safety endpoints

For all safety analyses, the respective safety set will be used. All listings and tables will be presented by treatment group. Safety summary tables will include only data from the on-treatment period (i.e. starting from the time point of first administration of the study medications) with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries).

Safety endpoints for Study Treatment Period 1:

- Patient incidence of AEs by system organ class and preferred term
- Fracture rates of any vertebral, nonvertebral, hip and all fractures will be summarized descriptively by treatment. Rates will be calculated for the number of fractures per patients and the number of patients with at least one fracture.
- Number of patients and incidence of fractures
- Number and grade of injection site reactions
- Changes from baseline in laboratory assessments (serum chemistry and hematology) and the shift between baseline and the worst value between baseline and completion of Week 52
- Changes from baseline in vital signs
- Summary of abnormal ECG values
- Patient incidence of antibodies to the study medications

Safety endpoints for Study Treatment Period 2:

- Patient incidence of AEs by system organ class and preferred terms
- Fracture rates of any vertebral, nonvertebral, hip and all fractures will be summarized descriptively by treatment. Rates will be calculated for the number of fractures per patients and the number of patients with at least one fracture.
- Number of patients and incidence of fracture
- Number and severity of injection site reactions
- Changes from baseline in laboratory assessments (serum chemistry and hematology) and the shift between start of Week 52 to completion of Week 78 and the worst value within this period
- Changes from baseline in vital signs
- Summary of abnormal ECG values
- Patient incidence of antibodies to the study medications within this period

Adverse events

All information obtained on AEs will be displayed by treatment group and patients.

The number (and percentage) of patients with treatment emergent AEs (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity) 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 medication related AEs, SAEs, and AEs leading to study discontinuation.

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

There is no planned statistical testing in the safety analyses.

Listing of death, SAEs, AEs leading to study drug discontinuation, AEs leading to study discontinuation and study drug related AEs will be provided.

Vital signs

Summary statistics will be provided by treatment group and visit.

Clinical laboratory evaluations

All abnormal clinically relevant laboratory data will be listed by treatment group, patient, and visit. Summary statistics of relevant laboratory parameters will be provided by treatment group and visit either numerically or graphically.

Shift tables using the low/ normal/ high (low and high) classification will be used to compare baseline to the worst on-treatment value for relevant laboratory parameters.

12-lead ECG

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

Immunogenicity

The incidence of patients who develop binding and neutralizing anti-drug antibodies (ADAs) by visit will be compared descriptively

12.6.3 Pharmacokinetics

Descriptive summary statistics of drug serum concentrations will be provided by treatment group and visit/ sampling time point.

Concentrations below LLOQ will be treated as zero in summary statistics. Geometric means will not be reported if there are values below the limit of quantification. Summary statistics will be presented at each visit, as well as a summary figure of mean concentrations over time by treatment group.

The bioequivalence of the secondary PK endpoints AUCinf and Cmax (EMA) will be assessed descriptively by calculating ratios of the geometric means and 90% CIs.

The analyses will be performed on the PKS.

12.6.4 Pharmacodynamics

The bioequivalence of the secondary PD endpoint (FDA/ PMDA) will be assessed in the same way as the primary PD endpoint as described in Section 12.5.2.2. The assessment of bioequivalence will be based upon the CIs (90% for FDA and 95% for PMDA) of the ratio of the geometric means (test/reference) 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 [0.80, 1.25].

For Treatment Period 1 (Day 1 to Week 52) CTX and procollagen I N-terminal propeptide (PINP) serum concentrations values will be analyzed descriptively per scheduled visit until completion of Week 52.

These analyses will be performed on the PDS.

For Treatment Period 2 (Week 52 to Week 78) CTX and PINP serum concentrations values will be analyzed descriptively per scheduled visit between the start of Week 52 and completion of Week 78. This will be performed for the TP2 FAS.

Serum CTX concentrations below LLOQ will be treated as LLOQ in summary statistics.

12.7 Interim analyses

Timing and purpose of data analyses is described in Section 4.4.

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.

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", "Continued Prolia" and "transition into 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 CSR for the final analysis at Week 78 will be cumulative and also include the primary analysis from Week 52.

12.8 Sample size calculation

The required sample size was calculated using SAS 9.4.

12.8.1 Assumptions of sample size calculation

The calculations were based on the following assumptions.

Table 12-9 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)

The correlation between the PK parameters and the PD/ efficacy parameters is assumed to be zero. Most likely there is a correlation between PK and PD endpoints but it is difficult to estimate the value a-priori and setting it to zero leads to a conservative estimate of the power.

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 12-10.

Table 12-10 %CfB in LS-BMD at 12 months for denosumab 60 mg 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 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 Prolia data. The correlation between Cmax and AUCinf is an assumption and the true value of the correlation is likely to be higher. However, again this leads to a conservative estimate of the power.

The sample size was calculated for both the FDA, and combined EMA/ PMDA requirement in a joint calculation, i.e. the statistical power of meeting all co-primary endpoints was considered.

12.8.2 Margin derivation for %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 12-10) and has been agreed with FDA, EMA and PMDA as appropriate. Information used in the meta-analysis to derive the margins are presented in Table 12-11.

Table 12-11 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 trial (Cummings et al 2009)	5.5	0.1308	7.6479
2	McClung et al 2006	5.35	0.4519	2.2131
3	DEFEND trial (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 12-10

* calculated as $\sum_{i=1}^{3} w_i x_{di} / \sum_{i=1}^{3} w_i$ applying inverse variance weighting

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

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 approach)
- A margin of 2.00% retains more than 50% of the minimum treatment effect (EMA and PMDA approach)

12.8.3 Combined sample size calculation

Table 12-12 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 12-9.

Table 12-12 Testing specifications for combined requirements

Requirement	FDA %CfB in LS-BMD[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 treatments	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			

[1]. The FDA for %CfB in LS-BMD requirement is more stringent and hence EMA and PMDA requirement are not shown.

100,000 samples of sample size of 418 evaluable patients (209 evaluable patients per arm) were generated from a multivariate normal distribution as defined in Table 12-9 leading to a sample size of 492 patients (246 per arm). Using the testing requirements defined in Table 12-12 each co-primary endpoint was tested for each random sample. If all four tests were passed then the sample was a success. The overall power was estimated as the percentage of successes out of the 100,000 random samples. Using the above simulation a power of 90.4% for simultaneously passing all the equivalence tests for the co-primary endpoints was obtained.

Treatment Period 2

The analysis of the Treatment Period 2 is only descriptive and therefore no formal sample size calculation is conducted for the Treatment Period 2.

12.8.4 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%.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/ institution must obtain approval/ favorable opinion from the Institutional Review Board/ Independent Ethics Committee (IRB/ IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/ her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to sponsor monitors, auditors, sponsor Quality Assurance representatives, designated agents of the sponsor, IRBs/ IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the sponsor immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT (European Union Drug Regulating Authorities Clinical Trials database). In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the sponsor publication policy including authorship criteria, please refer to the sponsor publication policy training materials that were provided to you at the trial investigator meetings.

Any data analysis carried out independently by the investigator should be submitted to the sponsor before publication or presentation.

13.4 Quality control and quality assurance

Sponsor maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures (SOP) as well as applicable global/ local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and sponsor systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/ risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written sponsor processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to the sponsor and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/ IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, health authorities where required, and the IRB/ IEC prior to implementation.

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/ IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action and the IRB/ IEC at the study site should be informed according to local regulations.

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16 Appendices

Not applicable.