Statistical Analysis Plan

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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	12Aug2020	
Amendment 1 (v2.0)	15Apr2023	1. Section 6.4: replace the PD analysis set with BTM analysis set. Subjects should have least a baseline BTM measurement of interest and at least 1 post-baseline BTM measurement of interest. 2. Section 8.3: table 8.1 is removed. Missing stop date of AE or CM will not imputed. Imputation for start date of AE or CM is outlined in Appendix B.

		3. Section 9.2: The disposition of all randomized subjects will be tabulated by cohort is replaced with “The disposition of all subjects will be tabulated by cohort”. 4. Section 9.4: unit of BMI is revised to kg/m^2. (Yes, No) is removed from use of vitamin D and calcium. Nonvertebral fracture is added for fracture history and the definition of historical nonvertebral fractures is added as well. The error reference source for section 6.1 is addressed. 5. Section 9.5.2: add reference hyperlink for Letocha et al, 2005, Rauch et al, 2009 and Ward et al, 2011. 6. Section 9.5.2: Graphs showing summary statistics (actual value and change) of BMD Z-score, and percent change from baseline of BMD at lumbar spine over time by visit for age groups will be provided. 7. Section 9.6.1: Subject listing of treatment-emergent adverse event will be provided. summary for subject incidence of adverse event is added. Serious cardiovascular event will be identified using cardiac and vascular SOC in MedDRA and be summarized as EOI. 8. Section 9.6.2: Graphs depicting summary statistics (change or percent

		change from baseline) for each parameter over time will be provided. 9. Section 9.6.6: Shifts in severity grades of laboratory parameters will not be assessed. Evaluation for Hy's Law and definition is added. 10. Section 9.6.6: Graphs showing central tendency and dispersion of the absolute values and percent changes from baseline by visit will also be provided for the following laboratory parameters: calcium corrected by albumin, phosphorus and alkaline phosphatase. 11. Section 9.6.8: Descriptive statistics will be produced to describe the exposure to IP by cohort is added. 12. Section 10: Shifts in laboratory parameters between baseline and the most extreme post baseline values will be assessed base on Severity Intensity Scale for Adverse Events. However, the laboratory abnormality with clinical significance is considered as adverse event. Therefore, the grade shifts in laboratory parameters will not be conducted. 13. Appendix A: per protocol, nominal visit Day 8 is added for 12-lead ECG and the Day 29 in footnote is replaced with Day 8; Day 61 is removed for vital sign.

		14. Appendix B. Handling of Dates, Incomplete Dates and Missing Dates is added. The imputation rules for partial or missing start dates are outlined.

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMC	bone mineral content
BMD	bone mineral density
BP	bisphosphonate
BTM	bone turnover markers
C_{max}	maximum-observed concentration
CRF	case report form
DILI	drug-induced liver injury
DLRM	dose level review meeting
DLRT	dose level review team
DXA	dual-energy X-ray absorptiometry
eCRF	electronic case report form
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IP	investigational product
iPTH	Intact Parathyroid Hormone
Kg	kilogram
Mg	milligram
P1NP	procollagen type 1 N-terminal propeptide
PD	pharmacodynamic
PI	principal Investigator
PK	pharmacokinetic

SC	subcutaneous
sCTX	Serum type I collagen C-telopeptide
Source Data	Information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
T_{max}	time to C_{max}

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20160227, Romosozumab dated 28 February 2023. The scope of this plan includes the primary analysis that is planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the pharmacokinetics (PK) profile following multiple SC doses of romosozumab in children and adolescents with OI	• Romosozumab serum PK parameters maximum-observed concentration (C_{max}), time to C_{max} (t_{max}), area under the curve (AUC), and terminal half-life ($t_{1/2}$)
Secondary	
• To evaluate the safety, tolerability, and immunogenicity profile following multiple SC doses of romosozumab in children and adolescents with OI • To evaluate the pharmacodynamic (PD) profile following multiple SC doses of romosozumab in children and adolescents with OI	• Treatment-emergent adverse events, including events of injection site reactions and changes in cranial nerve function • Vital signs, electrocardiograms, physical examinations and safety laboratory tests, including serum calcium and phosphorous • Incidence of antiromosozumab antibodies • Actual value and percent change from baseline of bone turnover markers including serum P1NP and serum CTX measurements • Actual value and percent change from baseline of lumbar spine BMD, bone mineral content (BMC), and bone area • The percent change from baseline in BMD Z-score at lumbar spine

2.2 Hypotheses and/or Estimations

Romosozumab PK and PD, including the effects on bone mineral density (BMD) and bone turnover markers (procollagen type 1 N-terminal propeptide [P1NP] and serum collagen type 1 cross-linked C-telopeptide [CTX]), will aid in the selection of the dose for the subsequent efficacy and safety study in pediatric subjects with OI. Romosozumab will be safe and well tolerated following multiple SC dose administrations in children and adolescents with OI.

3. Study Overview

3.1 Study Design

This is a multicenter, open-label, ascending multiple-dose study to evaluate romosozumab in ambulatory children (5 to less than 12 years of age) and adolescents (12 to less than 18 years of age) with OI.

At least 16 subjects will be enrolled into sequential cohorts 1 to 4 (4 per cohort). All subjects will receive a total of [redacted] SC doses of romosozumab administered every [redacted]. Subjects in cohorts 1 (12 to less than 18 years of age) and 2 (5 to less than 12 years of age) will be administered romosozumab [redacted] mg/kg SC [redacted] Subjects in cohorts 3 (12 to less than 18 years of age) and 4 (5 to less than 12 years of age) will receive romosozumab [redacted] mg/kg SC [redacted] If the exposure and PD effects are insufficient at [redacted] and [redacted] mg/kg, at least 4 subjects each will enroll into cohorts 5 (12 to less than 18 years of age) and 6 (5 to less than 12 years of age) and will receive romosozumab [redacted] mg/kg SC [redacted] All subjects will receive daily supplementation with calcium and vitamin D.

The planned dose levels and cohorts are described in the below table.

Table 3-1. Planned Dose Levels

Cohort #	Age Group (years of age)	Dose*	Dosing Day	N (active)
1	12 to less than 18	[redacted]		4
2	5 to less than 12			4
3	12 to less than 18			4
4	5 to less than 12			4
5 (optional)	12 to less than 18			4
6 (optional)	5 to less than 12			4

* All doses will be administered subcutaneously

As a precautionary measure consistent with pediatric research, dose cohorts, starting with the lowest dose level, will be recruited so that adolescents 12 to less than 18 years of age will be enrolled first (n = 4) at each dose level, before children 5 to less than 12 years of age (n = 4) for the same dose level.

A dose level review meeting (DLRM) will be held to review safety data for the purposes of making recommendations before escalation to the next higher dose or expansion to a younger age cohort. The dose level review team (DLRT) will be composed of, at a minimum, the investigators actively enrolling subjects at the time of the meeting (ie, have subjects in screening or already enrolled), the Amgen Medical Monitor, and Amgen Global Safety Officer or designated safety scientist, Amgen Clinical Research Study Manager or designee, and biostatistics representative or designee. Additional members may be added as needed (eg, PK scientist). The DLRT voting members include the principal investigator or designee, Amgen Medical Monitor and Amgen Global Safety Officer or designee. The DLRT voting members are responsible for making dosing recommendations, which may include escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), de-escalation to a lower dose; continuation, delay, or termination of dosing; or repetition or expansion of a cohort. Clear stopping rules will be followed, and ad hoc DLRMs will be held if necessary. All available study data, including demographics, medical history, concomitant medications, adverse events, electrocardiograms, vital signs, and clinical laboratory test results will be reviewed. The medical monitor will review data on an ongoing basis throughout the duration of the study.

Investigators who are not actively enrolling subjects at the time of the DLRM will not participate in the DLRM. They will be informed of the DLRT recommendations.

DLRMs will take place at the following time points:

- DLRM 1
  - After 2 subjects in cohort 1 complete 6 weeks on study
  - DLRM 1 will enable enrollment into cohorts 2 and 3
- DLRM 2a
  - May be conducted if escalation to the [redacted] mg/kg dose level is deemed necessary based on available PK and PD data from cohorts 1 and 3
  - If necessary, DLRM 2a will be conducted after 2 subjects in cohort 3 complete 6 weeks on study
  - DLRM 2a will enable enrollment into cohort 5
- DLRM 2b
  - After 2 subjects in both cohorts 2 and 3 complete 6 weeks on study
  - DLRM 2b will enable enrollment into cohort 4
- DLRM 3
  - May be conducted if escalation to the [redacted] mg/kg dose level is deemed necessary based on available PK and PD data from cohorts 1 through 4

- If necessary, DLRM 3 will be conducted after 2 subjects in both cohorts 4 and 5 complete 6 weeks on study
- DLRM 3 will enable enrollment in cohort 6

3.2 Sample Size

The sample size is based on practical considerations. At least 16 subjects (or 24 depending on emerging results) will be enrolled into the study.

3.3 Adaptive Design

Adaptive design is not applied in the study.

4. Covariates and Subgroups

4.1 Planned Covariates

No covariate is planned in the study.

4.2 Subgroups

No subgroup analysis is planned.

5. Definitions

5.1 Basic Definitions

Treatment-emergent Adverse Events (TEAE)

Adverse Events (AEs) starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose on the Adverse Events eCRF and up to the end of study date.

Treatment-emergent Serious Adverse Event (TESAE)

Treatment-emergent adverse events indicated as serious on the Events eCRF

5.2 Study Points of Reference

Baseline

The baseline measurement is defined as the last measurement prior to the first dose of IP. If the measurement is taken on the same day as the first dose and the exact measurement time relative to the first dose is unknown, it will be assumed to have been taken prior to the first dose of IP. If a subject does not receive IP, baseline is the closest recorded measurement on or prior to the enrollment date.

Note: If baseline result from DXA assessment is not available, the results assessed on or before Study Day 14 will be considered baseline.

Study Day 1

Day 1 is defined as the first day that investigational product is administered to the subject. The day before Day 1 is referenced as Day -1.

Study Day

Post day of dose: study day= (study date - date of study Day 1) +1

Pre day of dose: study day= (study date – date of study Day 1)

The day prior to the first investigational product dosing is Day -1 while the day of the first investigational product dose is Day 1.

Analysis Visit

To allow for variations in scheduling study visits, the analysis visit windows defined in Appendix A will be used to assign evaluations to the most appropriate nominal visit for analysis and summarization.

5.3 Study Dates

Informed Consent Date

The date on which a subject signed the informed consent.

Enrollment Date

The date of enrollment in eCRF.

First Dose Date

The date of administration of the first dose of IP.

Last Dose Date

The date of administration of last dose of IP

End of the [redacted] Treatment Period Date

The end of the [redacted] treatment period date is defined as the date of the last assessment at the [redacted] visit. For subjects who discontinue from the study before completing the [redacted] visit, the end of study date is used for the end of the [redacted] treatment period end date. For those subjects who missed the [redacted] visit but did not terminate the study early, the target day [redacted] plus 3 days will be used as the end of the [redacted] treatment period date.

Start of the Follow-up Period Date

The start of the follow-up period date is defined as the end of the [redacted] treatment period date plus one day.

End of the Follow-up Period Date

For subjects with non-missing start of the follow-up period date, the end of the follow-up period date is defined as the end of study date as recorded on the electronic case report form (eCRF).

End of Study Date

The date recorded on the End of Study electronic case report form (eCRF)

5.4 Study Time Intervals

Screening Period

The time period between the date of informed consent and first dose of IP.

On-Study Period

The time period from the enrollment date to the end of study date, inclusive.

Treatment Period

The time period from the first dose date to the end of the [redacted] treatment period date Inclusive.

Follow-up Period

For subjects entering in the [redacted] follow-up period: the time period from the start of follow-up period date to the end of study date, inclusive.

5.5 Subject Disposition

Enrolled

Individuals are considered enrolled when the investigator confirms that the subject has met all eligibility criteria (both screening and day 1 pre-dose assessments). Enrolled individuals are referred to as “subjects”.

Exposed to IP

Subjects are considered exposed to IP if they have a value for the sum of IP volume that exceeds zero.

5.6 Arithmetic Calculations

Change from Baseline

The arithmetic difference between a post-baseline value and the baseline value:

Change (absolute) from Baseline = (post-baseline value – baseline value)

Change (percent) from Baseline = [(post-baseline value – baseline value) / baseline value] x 100

Body Mass Index (BMI)

Body Mass Index will be calculated using the following formula:

BMI (kg/m^2) = weight (kg) / [height (cm)/100]^2

Subject Incidence for AEs

The subject incidence for a given event in a given time period is defined as the number of subjects with at least 1 reported occurrence of the event divided by the number of subjects who are at risk for having the event at the beginning of the given time period. For subjects with multiple occurrences of the same event, the event will only be counted once per subject.

6. Analysis Sets

6.1 Full Analysis Set

The full analysis set (FAS) is defined according to intent-to-treat analysis to include all subjects enrolled into the study

6.2 Safety Analysis Set

The safety analysis set (SAS) includes all subjects in the FAS who received as least one (1) dose of investigational product.

6.3 PK Analysis Set

The PK analysis set will consist of all subjects for whom at least one (1) PK parameter or endpoint can be adequately estimated.

6.4 Bone Turnover Marker Analysis Subset (PD Analysis Set)

The bone turnover marker analysis set will consist of all subjects for whom at least a baseline BTM measurement of interest and at least 1 post-baseline BTM measurement of interest.

6.5 Bone Mineral Density (BMD) Analysis Set

The bone mineral density (BMD) analysis set includes subjects in the FAS who have a baseline lumbar spine DXA BMD measurement and at least 1 post-baseline lumbar spine DXA BMD measurement.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

No interim analysis is planned; however, Amgen, in consultation with the investigators, will review all available accumulating data before making dose escalation recommendations. Once the data becomes available, dose-aggregate and per subject PK data will also be reviewed, but it will be ensured that results do not reveal individual treatment assignments.

7.2 Primary Analysis

Please refer to Section 7.3.

7.3 Final Analysis

The final analysis will occur after all subjects have completed the study. The objective of the final analysis is to evaluate the safety and PK data and the final analysis will be performed at the end of the trial. All data will be cleaned and a database lock will occur.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

The following imputation for missing or incomplete data will be performed if required: Non-pharmacokinetic measurements (e.g., biomarker data) that are below the lower limit of quantification will be considered equal to half of the lower limit of quantification for all analyses unless specified otherwise.

Serum PK concentrations below the lower limit of quantifications will be set to zero for the estimation of the PK parameters for each subject and for the calculation of the

summary statistic for each time point. However, missing PK concentrations will not be imputed.

No imputation will be done on incomplete stop date of an AE or a concomitant medication.

Missing and incomplete start dates of an adverse event or concomitant medication taken will be imputed as outlined in Appendix B.

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations in each cohort. Other factors that may bias the results of the study include

- Important protocol deviations likely to impact the tolerability, safety analysis and interpretation of the endpoints as well
- Detection of adverse events and/or serious adverse events likely to impact the safety analysis
- The timing of and reasons for early withdrawal from treatment and from study

8.5 Outliers

Pharmacokinetic (PK) serum concentration data will be evaluated for outliers by visual inspection and decisions to re-assay individual samples will be made in accordance with standard pharmacokinetic evaluation practice. Histograms will be examined to identify outliers in any of the continuous variables used in the analyses. Unexpected and/or unexplained values in categorical data will be identified by utilizing frequency tables. Outliers due to data entry errors will be corrected by the study team before final database lock. The validity of any questionable values or outliers will be confirmed. Outliers or any questionable values with confirmed validity will be included in the analyses. All confirmed outlier data will be included in the analyses presented in this statistical analysis plan unless there is sufficient scientific justification (e.g., important protocol deviation leading to invalid data) to exclude them.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required data transformations will be utilized.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Descriptive statistics will be provided for selected subject disposition, demographics, safety, PK, and PD end points. Descriptive statistics on continuous measurements will include means, medians, standard deviations, quartiles (Q1, Q3) and minimum and maximum, while categorical data will be summarized using frequency counts and percentages. Data will be presented and summarized by cohort and visit as appropriate. Graphical summaries of the data may also be presented. When data are summarized by visit, the values recorded against the scheduled visits listed in the protocol will be used. When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used. In general, data listings will be sorted by, dose, subject and visit unless specified otherwise.

9.2 Subject Accountability

The disposition of all subjects will be tabulated by cohort. The subjects who received investigational product, completed investigational product, discontinued investigational product and reasons for discontinuing, completed study and discontinued study and reasons for discontinuing will be summarized in number and percentage.

Key study dates for the first subject enrolled, last subject enrolled, last subject end of investigational product and the last subject end of study will be presented.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

9.4 Demographic and Baseline Characteristics

Demographic (ie, collected age (years), sex, race, ethnicity (Hispanic, non-Hispanic), body composition (height [cm], weight [kg], BMI [**kg/m^2**])) and baseline disease

characteristics (ie, lumbar spine BMD, bone mineral content (BMC), bone area, and BMD Z-score, bone turnover markers (sCTX, P1NP), laboratory parameters (calcium corrected by albumin, phosphorus, creatinine, serum 25-OH vitamin D, eGFR), iPTH, fracture history (Any historical fracture (Yes, No), **nonvertebral fracture**), baseline use of vitamin D, baseline use of calcium, prior osteoporosis medication use (Yes, No), type of OI (I, II, III, and IV) will be summarized by cohort using descriptive statistics based on the Full Analysis Set defined in Section **6.1**.

Historical nonvertebral fractures are as reported on fracture history eCRF, excluding skull, facial, mandible, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, metacarpus, finger phalanges, and toe phalanges and fractures associated with high trauma or pathologic fractures.

9.5 PK and Efficacy Analyses

9.5.1 Analyses of Primary Endpoint(s)

Serum romosozumab concentrations will be determined using a validated assay. Individual serum concentration-nialtime plots for romosozumab will be presented for each subject as well as mean concentration-time plots for each dose cohort. PK parameters will be estimated using non-compartmental methods. Actual dosing and sampling times will be used for calculation of PK parameters. Summary statistics will be generated for each PK parameter for each dose cohort. The PK analysis set will be used to for these analyses.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Actual value and percent change from baseline in BMD, BMC and bone area at the AP lumbar spine will be descriptively summarized at each visit for each dose cohort. The change from baseline in BMD Z-score at lumbar spine will be checked against weighted estimated mean (SE) of 0.01 (0.09) (95%CI: -017, 0.18) based on meta-analysis from historical controls (**Letocha et al, 2005**; **Rauch et al, 2009**; **Ward et al, 2011**). **Graphs showing summary statistics (actual value and change from baseline) of BMD Z-score, and percent change from baseline of BMD at lumbar spine over time by visit for age groups will be provided**. The results from the historical controls will contextualize the observed BMD results at the dose level review meeting. The BMD analysis set will be used to for these analyses.

9.6 Safety Analyses

9.6.1 Adverse Event

The Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of

investigational product, fatal adverse events, and adverse events of interest. The severity grade of all treatment-emergent

adverse events will be summarized based on Severity Intensity Scale for Adverse Events.

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in descending order of frequency. Subject listing of all treatment-emergent adverse events will also be provided.

Subject incidence of events of interest (EOI; standardized MedDRA queries and/or Amgen customized queries) will also be summarized according to their categories and preferred term. Events of interest of hypersensitivity and malignancy will be identified using a narrow search/scope in standardized MedDRA queries (SMQ). Event of interest of hypocalcemia, injection site reaction, hyperostosis and osteoarthritis will be identified using Amgen-defined MedDRA search strategies. **Serious cardiovascular adverse events will be identified using cardiac and vascular system organ class (SOC) in MedDRA.** Adjudicated-positive adverse events of osteonecrosis of the jaw (ONJ) will also be summarized as EOIs.

The number and percentage of subjects reporting adverse events will be evaluated for each dose cohort, across dose cohorts, and will also be tabulated by relationship to study drug. In addition, summary of cranial nerve examination at each visit and the result change from entry exam over time for each cohort will be tabulated.

9.6.2 Bone Turnover Markers

Actual values and percent changes from baseline in each parameter (P1NP and sCTX) will be descriptively summarized for each dose cohort at each visit. **Graphs depicting**

summary statistics (change or percent change from baseline) for each parameter over time will be provided. The PD analysis set will be used to for the analyses.

9.6.3 Vital Signs

Vital signs will be reviewed for each subject. Depending on the size and scope of changes, summaries of vital sign data over time and/or changes from baseline over time may be provided. The safety analysis set will be used to for the analyses.

9.6.4 ECG

ECG data will be listed and reviewed for each subject. Depending on the size and scope of changes, summaries of ECG data over time and/or changes from baseline over time may be provided.

9.6.5 Physical Examinations

Height and weight data will be reviewed for each subject. Individual subject results will be examined in relation to baseline recordings. Depending on the size and scope of changes in data, summaries of physical examinations data over time and/or changes from baseline may be provided.

9.6.6 Safety Laboratory Tests

Actual values and changes from baseline in each parameter will be descriptively summarized each dose cohort at each visit. For serum calcium, phosphorous, and magnesium, the percent change from baseline also will be provided. All laboratory analyses will be based on the safety analysis set.

Graphs showing central tendency and dispersion of the absolute values and percent changes from baseline by visit will also be provided for the following laboratory parameters: calcium corrected by albumin, phosphorus and alkaline phosphatase.

Table 9-1. Safety Laboratory Test Panel

Laboratory: Chemistry	Laboratory: Hematology
albumin alkaline phosphatase (ALP) ALT (SGOT) AST (SGPT) bicarbonate (HCO3) direct bilirubin total bilirubin blood urea nitrogen creatinine creatine kinase chloride magnesium phosphorous potassium Sodium total protein glucose 25-OH vitamin D iPTH calcium albumin-corrected calcium	red blood cells Hemoglobin Hematocrit mean corpuscular volume (MCV) mean corpuscular hemoglobin (MCH) mean corpuscular hemoglobin concentration (MCHC) platelet count white blood cells • total neutrophils • eosinophils • basophils • lymphocytes • monocytes

Drug-induced liver injury will be assessed by evaluating subjects for Hy's Law. Hy's law laboratory criteria are defined as aspartate transaminase or alanine transaminase > 3 times upper limit of normal (ULN), total bilirubin > 2 times ULN, and alkaline phosphatase < 2 times ULN assessed within 7 days.

9.6.7 Anti-romosuzomab Antibodies

Immunogenic response during the study will be described by tabulating the numbers and percentages of subjects who tested positive for (binding and neutralizing) anti-romosuzomab antibodies based on the safety analysis set.

9.6.8 Exposure to Investigational Product

Subject listing of manufacturing lot numbers and a separate listing of unique manufacturing lot numbers used in this study will be provided. Details for each romosuzomab administration will be listed for every subject.

Descriptive statistics will be produced to describe the exposure to IP by cohort.

10. Changes From Protocol-specified Analyses

According to Section 10.4.3.6 in protocol version superseding amendment 3 dated 28 February 2023, **shifts in laboratory parameters between baseline and the most extreme post baseline values will be assessed base on the Severity Intensity Scale for Adverse Events. However, the laboratory abnormality with clinical significance is considered as adverse event. Therefore, the grade shifts in laboratory parameters will not be conducted.**

11. Literature Citations / References

Letocha AD, Cintas HL, Troendle JF et al. Controlled trial of pamidronate in children with type III and IV osteogenesis imperfecta confirms vertebral gains but not short-term functional improvement. *Clin Trial*. 2005; 20(6): 977-86.

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12. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

For the baseline assessment (excluding DXA), regardless of the width of the visit window, if there are multiple records within a Baseline window, the record that is the closest to and on or prior to Study Day 1 will be considered as the baseline value.

For the post-baseline assessment, if more than 1 visit falls within the defined window, the result from the visit closest to the target day will be used. If 2 evaluations are of the same distance from the target day, the result from the later visit will be used. If more than one evaluation on the same date, the average of the results will be used. Only laboratory results collected from the central laboratory will be averaged in the case of duplicate results.

To allow for variations in scheduling, the following visit windows will be used to assign evaluations to a most appropriate nominal visit for analysis and summarization. Furthermore, there will be no gaps between visit windows in order to include as many data points as possible for summarization.

Spine DXA Scans

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline[a]	1	Last evaluation prior to or on Study Day 1
Day 85	85	Study Day 2 to 127
EOS	169	Study Day 128 to End of Study

[a]If results from baseline DXA are not available, the results from scans taken on or before Study Day 14 will be considered baseline values and not the Day 85 values.

Physical Examination and Facial Nerve Examination

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline[a]	1	Last ealuation prior to or on Study Day 1
Day 57	57	Study Day 2 to 71
Day 85	85	Study Day 72 to 127
EOS	169	Study Day 128 to End of Study

[a]Any assessment done on Study Day 1 but after the administration of the investigational product will be classified into Day 57.

12-lead ECG

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline[a]	1	Last evaluation prior to Study Day 1
Day 8	**8**	**Study Day 2 to 18**

Day 29	29	Study Day 19 to 99
EOS	169	Study Day 100 to End of Study

[a]Any assessment done on Study Day 1 but after the administration of the investigational product will be classified into **Day 8**

Laboratory Assessments (Chemistry)

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline[a]	1	Last evaluation prior to or on Study Day 1
Day 8	8	Study Day 2 to 18
Day 29	29	Study Day 19 to 43
Day 57	57	Study Day 44 to 60
Day 64	64	Study Day 61 to 74
Day 85	85	Study Day 75 to 99
Day 113	113	Study Day 100 to 141
EOS	169	Study Day 142 to End of Study

[a]Any assessment done on Study Day 1 but after the administration of the investigational product will be classified into Day 8.

Laboratory Assessments (iPTH)

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline[a]	1	Last evaluation prior to or on Study Day 1
Day 8	8	Study Day 2 to 18
Day 29	29	Study Day 19 to 43
Day 57	57	Study Day 44 to 71
Day 85	85	Study Day 72 to 99
Day 113	113	Study Day 100 to 141
EOS	169	Study Day 142 to End of Study

[a]Any assessment done on Study Day 1 but after the administration of the investigational product will be classified into Day 8.

Laboratory Assessments (Hematology)

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline[a]	1	Last evaluation prior to or on Study Day 1
Day 29	29	Study Day 2 to 43
Day 57	57	Study Day 44 to 71
Day 85	85	Study Day 72 to 127
EOS	169	Study Day 128 to End of Study

[a]Any assessment done on Study Day 1 but after the administration of the investigational product will be classified into Day 29.

Weight

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline[a]	1	Last evaluation prior to or on Study Day 1
Day 29	29	Study Day 2 to 43
Day 57	57	Study Day 44 to 113
EOS	169	Study Day 114 to End of Study

[a]Any assessment done on Study Day 1 but after the administration of the investigational product will be classified into Day 29.

Height

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline[a]	1	Last evaluation prior to or on Study Day 1
EOS	169	Study Day 2 to End of Study

[a]Any assessment done on Study Day 1 but after the administration of the investigational product will be classified into Day 169.

Vital Signs

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline[a]	1	Last evaluation prior to or on Study Day 1
Day 29	29	Study Day 2 to 43
Day 57	57	Study Day 44 to 60
Day 64	64	Study Day 61 to 67
Day 71	71	Study Day 68 to 78
Day 85	85	Study Day 79 to 99
Day 113	113	Study Day 100 to 141
EOS	169	Study Day 142 to End of Study

[a]Any assessment done on Study Day 1 but after the administration of the investigational product will be classified into Day 29.

Serum PK and BTMs (sCTX and P1NP)

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline[a]	1	Last evaluation prior to or on Study Day 1
Day 8	8	Study Day 2 to 11
Day 15	15	Study Day 12 to 22
Day 29	29	Study Day 23 to 43
Day 57	57	Study Day 44 to 60
Day 64	64	Study Day 61 to 67
Day 71	71	Study Day 68 to 78
Day 85	85	Study Day 79 to 99
Day 113	113	Study Day 100 to 141
EOS	169	Study Day 142 to End of Study

[a]Any assessment done on Study Day 1 but after the administration of the investigational product will be classified into Day 8.

Antiromosozumab Antibody Assessments

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline[a]	1	Last evaluation prior to or on Study Day 1
Day 15	15	Study Day 2 to 22
Day 29	29	Study Day 23 to 57
Day 85	85	Study Day 58 to 127
EOS	169	Study Day 128 to End of Study

[a]Any antibody assessment done on Study Day 1 but after the administration of the investigational product will be classified into Day 15.

Appendix B. Handling of Dates, Incomplete Dates and Missing Dates

Imputation Rules for Partial or Missing Start Dates

The reference date for the following rules is the date of first dose of study drug.

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		Missing
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	2	2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1=Impute the date of first dose; 2=Impute the first of the month; 3=Impute January 1 of the year; 4=Impute January 1 of the stop year
Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month or first day of year if month is also missing.

Imputation Rules for Partial or Missing Death Dates

Incomplete or missing death dates will not be imputed.