Statistical Analysis Plan

Protocol Title:	Multicenter, Single-arm Open-label Extension Study to Assess Long term Safety and Efficacy of Current or Prior Treatment With Denosumab in Children/Young Adults With Osteogenesis Imperfecta
Short Protocol Title:	Open-label Extension of Study 20130173 of Denosumab in Children and Young Adults with Osteogenesis Imperfecta
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	10 October 2019	Not applicable
Amendment 1 (v2.0)	11 March 2022	This statistical analysis plan (SAP) is updated based on the protocol amendment 5 for Denosumab study 20170534 dated 02 February 2022 and the German country specific substudy protocol supplement dated 11 January 2022 to perform final analysis.
Amendment 2 (v3.0)	**27 Apr 2022**	**This statistical analysis plan (SAP) is updated to add the definition for German substudy safety analysis set.** **Added the visit window for renal laboratory.** **Added the imputation rules for concomitant medications.**

Table of Contents

Table of Contents 3

1. Introduction 8

2. Objectives, Endpoints and Hypotheses 8
   - 2.1 Objectives and Endpoints 8
   - 2.2 Hypotheses and/or Estimations 10

3. Study Overview 10
   - 3.1 Study Design 10
   - 3.2 Sample Size 12
   - 3.3 Adaptive Design 12

4. Covariates and Subgroups 12
   - 4.1 Planned Covariates 12
   - 4.2 Subgroups 12

5. Definitions 12
   - 5.1 Study points of Reference 12
     - 5.1.1 Baseline 12
   - 5.2 General Study Periods 14
     - 5.2.1 Screening Period 14
     - 5.2.2 Treatment Period 14
     - 5.2.3 End of Study/Safety Follow-up Period 14
   - 5.3 Subject Disposition 14
   - 5.4 Arithmetic Calculations 15
   - 5.5 Study Endpoints 16
     - 5.5.1 DXA Assessments 16
     - 5.5.2 Metaphyseal Index Z-score of the Distal Femur 17
     - 5.5.3 Dental Radiograms (Mandibular Shaping) 17
     - 5.5.4 Molar Eruption 18

6. Analysis Sets 18
   - 6.1 Full Analysis Set 18
   - 6.2 Safety Analysis Set 18
   - 6.3 Study-specific Analysis Sets 18
     - 6.3.1 DXA Analysis Set 18
     - [redacted] 18
     - 6.3.3 Metaphyseal Analysis Set 19
     - 6.3.4 German Substudy Safety Analysis Set 19

7. Planned Analyses 19
   - 7.1 Interim Analysis and Early Stopping Guidelines 19

7.2 Primary Analysis 19
7.3 Final Analysis 19

8. Data Screening and Acceptance 19
8.1 General Principles 19
8.2 Data Handling and Electronic Transfer of Data 19
8.2.1 Rollover of 20130173 CRF Data to 20170534 20
8.3 Handling of Missing and Incomplete Data 20
8.4 Detection of Bias 20
8.5 Outliers 21
8.6 Distributional Characteristics 21
8.7 Validation of Statistical Analyses 21

9. Statistical Methods of Analysis 21
9.1 General Considerations 21
9.2 Subject Accountability 22
9.3 Important Protocol Deviations 22
9.4 Demographic and Baseline Characteristics 22
9.5 Efficacy Analyses 23
9.5.1 Analyses of Primary Efficacy Endpoint(s) 23
9.5.2 Analyses of Secondary Efficacy Endpoint(s) 24
9.5.2.1 BMD Z score of lumbar spine and proximal femur 24
9.5.3 Analyses of Exploratory Efficacy Endpoint(s) 24
[redacted] 24
..... 24
9.6 Safety Analyses 24
9.6.1 Analyses of Primary Safety Endpoint(s) 24
9.6.2 Adverse Events 25
9.6.2.1 Adverse Events of Special Interest 26
9.6.3 Laboratory Test Results 27
9.6.4 Vital Signs 27
9.6.5 Physical Measurements 27
9.6.6 Antibody Formation 27
9.6.7 Exposure to Investigational Product 27
9.7 Other Analyses 27
9.7.1 Metaphyseal Index Z-Scores and Oral Hygiene 27
[redacted] 28

10. Changes From Protocol-specified Analyses 29

11. Literature Citations / References 30

12. Data Not Covered by This Plan..... 31

13. Appendices..... 32

List of Tables

Table 1. Treatment Headers/ Definitions for Study 20170534 16
Table 2. Treatment Headers/ Definitions for Study 20170534 16
Table 3. Primary Efficacy Endpoint Summary Table 24
Table 4. Secondary Efficacy Endpoint Summary Table 24
Table 5. Exploratory Efficacy Endpoint Summary Table 24
Table 6. Primary Safety Endpoint Summary Table 25

List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
AFF	Atypical femoral fractures
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMC	Bone mineral content
BMD	Bone mineral density
BMDS	Biomedical Data Stewardship Standard
BMI	Body mass index
[redacted]	
CRF	Case report form
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DXA	Dual X-ray absorptiometry
EDC	Electronic data capture
ET	End of treatment
FAS	Full analysis set
GSO-DM	Global Study Operations-Data Management
ICH	International Council on Harmonisation
IP	Investigational product
IPD	Important protocol deviations
IVRS	Interactive voice response system
MI	Metaphyseal index
MRI	Magnetic resonance imaging

Abbreviation or Term	Definition/Explanation
OI	Osteogenesis imperfecta
ONJ	Osteonecrosis of the jaw
PIP	Pediatric Investigational Plan
PK	Pharmacokinetics
Q6M	Once every 6 months
Q3M	**Once every 3 months**
SAP	Statistical Analysis Plan
SAS	Safety analysis set / Statistical Analysis System
SC	Subcutaneous
[redacted]	
SQ	Genant semiquantitative scoring system

1. Introduction

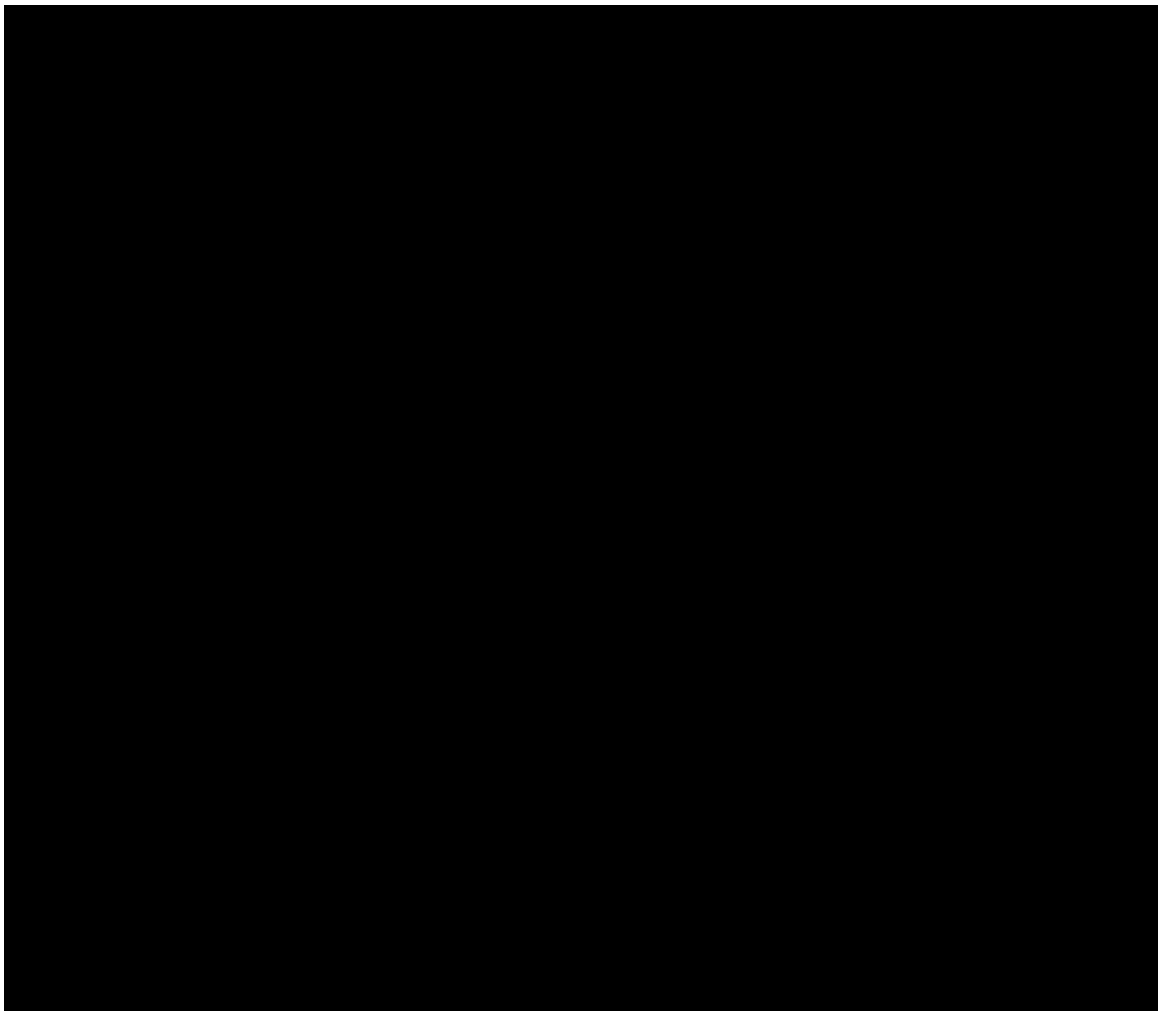
The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within protocol amendment 5 for study 20170534, AMG 162 Denosumab dated 02 February 2022. The scope of this plan includes the Final analyses and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate long-term safety of denosumab in subjects with pediatric osteogenesis imperfecta (OI) completing Study 20130173	The primary endpoints are subject incidence of adverse events, serious adverse events, and adverse events of special interest, subject incidence of anti-denosumab antibodies, changes from baseline in laboratory values and vital signs, and subject incidence of metaphyseal index Z score above age-appropriate normal range, abnormal molar eruption, and mandibular shaping
Secondary	
To describe changes in bone mineral density (BMD) of lumbar spine and proximal femur (total hip and femoral neck) from baseline to 6, 12, and 24 months.	Actual values and changes in BMD Z score of lumbar spine and proximal femur (total hip and femoral neck) from Study 20170534 baseline, as assessed by dual X-ray absorptiometry (DXA), at 6,12 and 24 months.

Exploratory
[redacted]



Objectives	Endpoints
[redacted]	

2.2 Hypotheses and/or Estimations

This study is descriptive in nature and does not involve testing formal hypotheses.

3. Study Overview

3.1 Study Design

Starting from 30 September 2021, due to the life-threatening events of hypercalcemia reported on denosumab use in the pediatric OI study, subjects will not receive any further dosing on 20170534 and will be followed for safety for 24 weeks following the last dose of denosumab**.** Study 20170534 is an open-label, prospective, extension study of Study 20130173 to assess long-term safety and efficacy of current or prior treatment with denosumab in children/young adults with OI. This study is required for compliance with key binding elements from the denosumab PIP for Study 20130173. All subjects who complete EOS on Study 20130173, regardless of whether they received investigational product until the last protocol-specified dose on the 20130173 study or ended investigational product early, are offered participation in a long-term open-label follow-up study – where this protocol has been approved at the site. Subjects who withdraw consent/assent to transition to 3-Month Dosing Regimen on 20130173 will also be offered participation in this study. When subjects in Study 20130173 near the EOS visit (completion), subjects will be offered participation in Study 20170534. If a subject is rolled over into the 20170534 study, they will be offered to receive alternative treatment including commercial denosumab every 6 months (6-Month Dosing Regimen) or will be observed without any treatment or the investigational product given every 3 months (3-Month Dosing Regimen). For subjects that consent/assent to participate in Study 20170534, Screening and study day 1 visit should coincide with Study 20130173 EOS

visit. Where this is not possible, the screening visit should occur on or within 28 days of the Study 20130173 EOS visit. Study day 1 should occur within 7 days from Screening.

Subjects enrolled in the study may be treated with denosumab or alternative osteoporosis medication/s at the discretion of the investigator, or may discontinue any osteoporosis medication for off-treatment observation. At any time during the study subjects may (1) discontinue denosumab, (2) resume denosumab (3-Month Dosing Regimen), (3) initiate alternative osteoporosis medication, and (4) discontinue alternative osteoporosis medication, based on the medical judgment of the investigator and per local standard of care (as applicable). In subjects who transition from denosumab to an alternative osteoporosis medication, the latter should be administered approximately **3** months after the last denosumab dose, ie, the next visit scheduled to receive study treatment, unless otherwise medically indicated. Similarly, transition from one standard of care osteoporosis medication to another or a reduced dose of denosumab should occur at the end of the dosing interval of the previous therapy. For subjects electing alternative therapy, alternative therapy may be administered by any qualified healthcare provider (HCP). The HCP must provide a written note to the subject describing the nature and date of alternative treatment to be documented by the investigative site. Subjects on alternative regimens given by HCPs other than investigational product, will continue to attend the study site every 6 months (weeks 12, 36, 60, and 84).

Subjects should return to the study site every 12 weeks (± 7 days) for treatment with denosumab. Subjects who are on observation only or on 6-Month dosing for alternative medications may attend scheduled visits every 24 weeks. For subjects receiving alternative osteoporosis medication/s, dosing frequency will be determined by the treatment regimen selected by the investigator, subjects will attend scheduled study visits every 6 months as per the Schedule of Activities. In this case, where a dosing visit does not coincide with a scheduled study visit, additional collection of assessments is not required other than recording of the medication on the concomitant medication eCRF page under alternative osteoporosis medication. All subjects should return for a final EOS/Early Termination visit.

Samples will be collected for clinical laboratory testing, including assessment of [redacted] and antidenosumab antibodies. Adverse events will be assessed throughout the study. Subjects will undergo annual DXA and radiographic assessments.

3.2 Sample Size

The number of subjects in this study will be determined by the number of subjects completing Study 20130173, and who are willing and able to participate in the long-term follow-up study.

3.3 Adaptive Design

Not applicable for this study.

4. Covariates and Subgroups

4.1 Planned Covariates

Not applicable for this study.

4.2 Subgroups

Not applicable for this study.

5. Definitions

5.1 Study points of Reference

5.1.1 Baseline

Study 20170534 baseline

For a given variable, the last measured value prior to administration of the first dose of denosumab or alternative osteoporosis medication/s in study 20170534 for subjects who will continue to receive denosumab or switch to alternative osteoporosis medication/s at start of 20170534, respectively, or the last measured value at Study 20130173 end of study visit for subjects who are observational only. Data collected after these specified timepoints will not be used for baseline.

The following study 20170534 baseline assessments will be conducted as part of the 20130173) end of study visit.

- Physical examination
- Tanner stage
- Vital signs
- Pregnancy test
- Hematology
- Chemistry
- [redacted]
- Antidenosumab-antibody
- Armspan

- DXA (AP lumbar spine)
- DXA (proximal femur – total hip and femoral neck in subjects ≥ 5 years of age)
- X-ray (lateral thoracic, lumbar spine)
- X-ray (AP knees)
- Dental X-ray (cephalogram and panoramic radiograph)
- Adverse events collection including clinical fracture recording
- Serious adverse events
- Concomitant medications

Above assessments from 20130173 end of study will be rolled-over as 20170534 screening assessments. Detailed roll-over procedures for adverse events, serious adverse events or concomitant medications are described in Section 8.2.1.

More generally, references to a study 20130173 measurement or milestone will always include the term “study 20130173”; therefore, any references to a timepoint without a study designation always refer to study 20170534.

Study Day 1

Study day 1 is defined as date of enrollment.

Study Day

The number of days from Study Day 1, inclusive:

Study Day = (Date of Interest – Date of Study Day 1 in 20170534 study) + 1

Visit Windows

See details in **Appendix C Analytical Windows**

Study dates

Informed Consent (IC) Date

The date on which the study informed consent form, and subject assent form if applicable, for study 20170534 is signed.

Screening Date

The screening date is the IC date of study 20170534.

Enrollment Date

The date on which the enrollment call for study 20170534 is made using IVRS.

End of Study Date

The date recorded on the End of Study eCRF.

5.2 General Study Periods

5.2.1 Screening Period

The time between date of informed consent and the enrollment date, inclusive. Subjects should enroll within 28 days from the Study 20130173 end of study visit, otherwise they will not be included in this study.

5.2.2 Treatment Period

The time between study day 1 and the date of month 24/ end of study visit, inclusive.

5.2.3 End of Study/Safety Follow-up Period

For subjects who discontinue study prior to month 24 visit, time between date of last protocol-required therapy or assessment visit and the safety follow-up date, inclusive.

5.3 Subject Disposition

Enrolled

Individuals are considered enrolled when an enrollment call is made using IVRS. Enrolled individuals are referred to as ‘subjects’.

Exposed to IP

Subjects are defined as exposed to IP if the total amount of IP volume received during the study is greater than zero.

Exposed to alternative osteoporosis medication/s

Subjects are defined as exposed to alternative osteoporosis medication/s if the total amount of any alternative osteoporosis medication volume received during the study is greater than zero.

Treatment Headers/ Definitions

Because of the study design that allows subjects at any time to discontinue denosumab, resume denosumab, initiate alternative osteoporosis medication, discontinue alternative osteoporosis medication or receive no treatment (observation only), the analysis of the 20170534 study will be based upon the respective baseline treatment and subsequent treatment paradigms (ie, it will be based on the subjects’ entire dosing trajectory). These groups are therefore not “as-randomized” and are not suitable for between-group formal statistical comparisons**.** Baseline/demog and safety data for the 20170534 study will be

summarized using the treatment headers and definitions as defined in Table 1. [redacted] BMD, protocol deviations, and antibody data will be summarized using any treatment defined in Table 2

Table 1. Treatment Headers/ Definitions for Study 20170534

Analysis Description	Treatment Header	Definition
Denosumab	1. Q3M Denosumab	Includes subjects who received at least one dose of Q3M denosumab in study 20170534
	2. Q6M Denosumab	Includes subjects who received at least one dose of denosumab, but no Q3M denosumab in study 20170534
Non-Denosumab	Alternative medications only / Observational	Includes subjects who received non-denosumab alternative therapy during study 20170534 or subjects who are not receiving any medication at 20170534 baseline.

Table 2. Treatment Headers/ Definitions for Study 20170534

Analysis Description	Treatment Header	Definition
Any Treatment	Q3M Denosumab / Q6M Denosumab / Alternative medications / Observational	Includes all subjects

5.4 Arithmetic Calculations

Age at Enrollment (Years)

Number of whole years from a subject's birth date to enrollment date as recorded on the study 20130173 eCRF if date is provided as DD/MM/YYYY or MM/YYYY, or number of years from a subject's birth year to the year of the enrollment date as recorded on the eCRF if date is provided as YYYY.

Age at Enrollment (Months)

Age in months is derived as collected age on screening period in years multiplied by number of months in year.

Age at Visit

Age at visit in years is derived as –

((visit date - Date of Birth) +1) / 365.25

If Date of birth is incomplete then use below formula,

Collected age at screening period in years + (visit date - screening date)+1 / 365.25

Age at visit in months is derived as –

((visit date - Date of Birth)+1) / 30.4375

If Date of birth is incomplete then use below formula,

Collected age at screening period in months + (visit date - screening date)+1 / 30.4375

Change from baseline

For a given variable, study baseline of interest, and timepoint of interest, subtract the endpoint value at the timepoint of interest minus the corresponding baseline value.

Percent Change from baseline

The change from baseline divided by study baseline value of interest and multiplied by 100:

(Change from Baseline/ Baseline) * 100

Subject Incidence Rate

The subject incidence rate for a given event in a given time period is defined as the number of subjects with ≥ 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 be counted once per subject.

5.5 Study Endpoints

5.5.1 DXA Assessments

All subjects will undergo bone densitometry assessments of the lumbar spine and subjects 5 years of age or older at screening will undergo bone densitometry assessments of the proximal femur (for total hip and femoral neck) performed by DXA. Scans will be performed at all applicable visits. Only GE Lunar or Hologic bone densitometers will be allowed for this study. The same DXA machine must be used for all DXA assessments for a particular subject. The left side should be used for proximal femur, unless prohibited (eg, hip implant). If another side must be used or is

inadvertently used during Screening, then the same side must be used consistently throughout the study.

Lumbar spine scans should include L1 through L4. Individual vertebral levels may be excluded due to artifact. A vertebral level excluded from one visit will be excluded from all visits with the total lumbar spine BMD calculated based on the evaluable vertebral levels. Baseline DXAs will be performed as duplicate scans; DXA assessments at all other visits will be performed as single scans. After analysis of the scans by the central imaging vendor, the study site may be asked to re-acquire a scan, because of poor positioning or other technical reasons.

5.5.2 Metaphyseal Index Z-score of the Distal Femur

To assess a subject's eligibility at screening, anteroposterior radiographs of both knees (unless prohibited by the presence of hardware such as implants) is to be used to calculate the metaphyseal index Z-score of each knee; the knee for assessment during the study at 6,12,18 and 24 months should be the one with the higher Z-score at baseline, unless prohibited by presence of hardware, in which case an anteroposterior radiograph of the contralateral knee may be obtained. Subject incidences of metaphyseal index Z-score above age-appropriate normal range (ie, metaphyseal index Z-score > +2) will be provided at each timepoint. The metaphyseal index (MI) will be calculated by the central imaging vendor as the ratio of the femoral width (W) over the distal femoral growth plate width (GPW), and the Z-score for each subject, relative to the subject's age as:

$$\text{MI Z-score} = (\text{subject value} - \text{mean})/\ \text{SD},$$

where mean and standard deviation (SD) are the corresponding values based on *Ward et al database,* (Ward, 2005), for the subject's age group at the time of the assessment.

5.5.3 Dental Radiograms (Mandibular Shaping)

Lateral cephalogram will be performed to enable assessment of mandibular shaping at Screening and 24 months. The lateral cephalogram is a profile X-ray of the skull and soft tissues and is used to assess the relation of the teeth in the jaws, the relation of the jaws to the skull, and the relation of the soft tissues to the teeth and jaws.

The following anatomical angles and dimensions will be measured to evaluate the correct proportions of the mandible and its position relative to the skull/maxilla:

- Gonial angle
- SNA angle

- SNB angle
- ANB Angle = SNA - SNB.

5.5.4 Molar Eruption

Radiographic assessment of molars will be performed at all visits. In addition, each subject will undergo a visual inspection under natural light for the presence of the first and second molars. Oral visual inspection should be performed at every 3 months to assess the risk for unerupted molars. The subject should be referred to a dentist to perform radiographic assessment of the unerupted molar(s) if:

- A subject is age 7 to 12 years and appears to have an unerupted upper or lower first molar (ie, not all 4 first molars are visible/detectable).
- A subject is age 13 years or older and appears to have an unerupted upper or lower (first or) second molar (ie, not all 4 first molars and all 4 second molars are visible/detectable).

For subjects 7 to 12 years of age, the number of 1st unerupted or partially erupted molars will be reported by visit. Likewise, for subjects 13 years of age or older, the number of 2nd unerupted or partially erupted molars will be reported by visit. Please note that the molars status refers to permanent molars only and age refers to age at visit.

6. Analysis Sets

6.1 Full Analysis Set

The full analysis set (FAS) includes all enrolled subjects who have provided informed consent/assent and have a non-missing enrollment date.

6.2 Safety Analysis Set

The safety analysis set (SAS) includes all subjects in the FAS who received ≥ 1 dose of denosumab during study 20130173.

6.3 Study-specific Analysis Sets

6.3.1 DXA Analysis Set

The DXA analysis set includes all subjects in the FAS with baseline and ≥ 1 postbaseline valid DXA assessments for the endpoint of interest (lumbar spine, total hip or femoral neck) as provided by the central imaging vendor. Note that this subset could potentially be different from endpoint to endpoint due to missing data.

[redacted]

6.3.3 Metaphyseal Analysis Set

This metaphyseal analysis set includes all subjects in the SAS with open growth plates (and no hardware preventing accurate calculation of metaphyseal index) at baseline and X-ray of the knee at baseline and postbaseline.

6.3.4 German Substudy Safety Analysis Set

The subset includes all subjects in the SAS who enroll in the German substudy.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Not applicable for this study.

7.2 Primary Analysis

Primary analysis will occur upon completion of the study when the last subject completes the 24-week follow-up visit following the last dose of denosumab.

7.3 Final Analysis

No final analysis is planned as the primary analysis will occur at the end of the study.

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, except for the imaging and laboratory data. This study will use the RAVE database. The central imaging vendor will provide DXA scans, and X-ray (lateral thoracic, knees, lateral cephalogram, and panoramic radiograms or radiographic assessment) data to Amgen cumulatively.

The central laboratory vendor will provide all lab-related data, except for the samples analyzed at local laboratories. All laboratory values will be transferred cumulatively from the central laboratory.

Data screening will be performed periodically during the conduct of the study. 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. Any questionable values or situations will be reported to GSO-DM for review or confirmation.

As part of the data acceptance procedure, all datasets, planned tables, listings, and graphs will be generated and reviewed to identify any additional data issues. Any critical issues identified must be resolved with GSO-DM before final acceptance of the data.

8.2.1 Rollover of 20130173 CRF Data to 20170534

Rollover program from 20130173 occurs only once for a patient when they complete 20130173 end of study visit, and are ready to be enrolled in 201**7**0534 study. Site calls IVRS to get patient created in RAVE for 20170534 study and provide 20130173 patient number to have same patient number in 20170534 eCRF.

The following eCRF forms/ variables will be rolled over from 20130173 to 20170534 at time of enrollment via IVRS,

- Sex, Ethnicity, Race
- Medical History
- Subject Fracture History
- Type and features of OI
- Concomitant Medications
- Adverse events
- SAEs
- Adjudication data
- Clinical Fracture Summary

Not all AEs from 20130173 study are expected to be recorded as medical history. It is investigator's decision on what events to enter onto medical history. Ongoing AEs/SAEs, ongoing concomitant medications and unresolved fractures at the time of Study 20170534 enrollment will be rolled over to 20170534. Resolved AEs, SAEs from Study 20130173 will be entered into Study 20170534 Medical History by site at the discretion of investigator. Adjudication data will only be transferred if an event is ongoing or if entered by site.

8.3 Handling of Missing and Incomplete Data

Missing and incomplete dates will be imputed as outlined in Appendix B.

8.4 Detection of Bias

Given the open-label nature of the study, changes to the study conduct and statistical analyses should be kept to a minimum to avoid undermining the study credibility. Any change to the protocol that is data driven should be avoided, except for safety related

events and changes related to inclusion/exclusion criteria to speed up enrollment, if needed.

Important protocol deviations likely to impact the analysis and interpretation of the endpoints will be tabulated in the Clinical Study Report (CSR).

If any sensitivity analyses are required to evaluate potential biases in the study's conclusions, the sources of the potential biases and results of the sensitivity analyses will be documented in the CSR.

8.5 Outliers

Scatter plots will be examined to identify outliers in continuous variables. Frequencies of the categorical data will be examined to identify questionable values. Outliers resulting from data entry error will be corrected in the database. Outliers that are not due to data entry error will be included in the analysis. The validity of any questionable values or outliers will be confirmed. No valid measurement will be excluded from analyses.

8.6 Distributional Characteristics

Not applicable for the study.

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 demographics and subject characteristics, efficacy, and safety data **.** Descriptive statistics of continuous measurements will include mean, standard deviation, minimum, 25th percentile, median (50th percentile), 75th percentile, maximum and number of nonmissing observations (n). Nominal and ordinal categorical variables will be summarized using counts and percentages.

Visit based on the observed values, with no imputation for missing values.

9.2 Subject Accountability

The disposition of all enrolled subjects will be tabulated. Disposition for number of enrolled subjects, successfully completing IP administration, and completing the study will be included. The disposition of subjects will also include the number of subjects who withdrew from the IP and their reasons for withdrawal and the number of subjects who withdrew from study and their reasons for withdrawal.

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.

Descriptive summary and listing of the IPDs will be generated for all the subjects during entire study.

9.4 Demographic and Baseline Characteristics

Subject demographic and baseline disease characteristics will be summarized based on FAS.They include the following endpoints:

- Race
- Ethnicity
- Age (in years)
- Age (in months)
- Age cohorts (2 to 6, 7 to 10, 11 to 17 years, as observed at screening in 20130173 study)
- Gender
- Body composition (height [cm], weight [kg], and BMI [kg/m^2])
- Armspan
- Vital signs (pulse, respiration rate, temperature)
- Select laboratory assessments

[redacted]

- DXA assessments of the lumbar spine and proximal femur (these DXAs will be performed as duplicate scans at 20170534 baseline only)

9.5 Efficacy Analyses

Table 3. Primary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
Not applicable		

Table 4. Secondary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
Actual values and changes in BMD Z score of lumbar spine and proximal femur (total hip and femoral neck) from Study 20170534 baseline, as assessed by dual X-ray absorptiometry (DXA), at **6**, 12 and 24 months	Summary statistics will be provided for actual and change from Study 20170534 baseline in BMD Z-score per skeletal site (lumbar spine, total hip and femoral neck), and by visit (6, 12 and 24 months). Analysis will be based on DXA analysis set.	Not applicable for this study.

Table 5. Exploratory Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
[redacted]		

9.5.1 Analyses of Primary Efficacy Endpoint(s)

Not applicable for the study.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Summaries for each secondary efficacy endpoints will be provided by time points of interest and treatment headers/definitions as applicable.

9.5.2.1 BMD Z score of lumbar spine and proximal femur

Summary statistics will be provided for actual values and change from study 20170534 baseline in BMD Z-score per skeletal site (lumbar spine, total hip and femoral neck) at 6,12 and 24 months. All analyses will be based on the site-specific DXA analysis set. Missing baseline and post-baseline BMD Z-scores will not be imputed.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

Summaries for each exploratory efficacy endpoints will be provided by visit as applicable.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Descriptive statistics will be provided for each safety endpoint by treatment category if data warrants.

Table 6. Primary Safety Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
Subject incidence of adverse events and serious adverse events	Subject incidence of any AEs, serious AEs, AEs leading to withdrawal of investigational product, AEs of special interest and fatal AEs will be tabulated by system organ class and preferred term in descending order of frequency using SAS and **Overall summary of AE's using** German substudy **safety** analysis set.	Not applicable for this study.

Subject incidence of anti-denosumab antibodies	Percentages of subjects who tested positive (binding or neutralizing) for antidenosumab antibodies will be descriptively summarized by visit for subjects in SAS and German substudy **safety** analysis set who continued with denosumab.	Not applicable for this study.
Changes from baseline in laboratory values and vital signs	Actual values and changes from baseline in each laboratory and vital signs parameter will be summarized at each visit. For serum calcium, phosphorus, and alkaline phosphatase (ALP), summary of the percent change from baseline will be provided for subjects in SAS and German substudy **safety** analysis set. Shifts in laboratory parameters between baseline and the most extreme post baseline values will be provided based on the SAS.	Not applicable for this study.
Subject incidence of metaphyseal index Z score above age-appropriate normal range	Subject incidence of the metaphyseal index Z-score above age-appropriate normal range safety events will be tabulated for subjects in SAS and German substudy **safety** analysis set	Not applicable for this study.
Subject incidence of abnormal molar eruption, and mandibular shaping	Subject incidence of the abnormal molar eruption safety events will be tabulated for subjects in SAS and German substudy **safety** analysis set **and descriptive summary statistics for mandibular shaping parameters will be tabulated for subjects in SAS and German substudy safety analysis set.**	Not applicable for this study.

[redacted]

9.6.2 Adverse Events

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. All adverse event tables will be summarized using the treatment headers as defined Table 1.

The subject incidence of adverse events will be summarized for adverse events, serious adverse events, adverse events leading to withdrawal of denosumab, fatal adverse events , and adverse events of special interest.

Subject incidence of all adverse events, serious adverse events, adverse events leading to withdrawal of denosumab, and fatal adverse events will be tabulated by system organ class and preferred term in descending order of frequency.

Subject incidence of events of interest (standardized MedDRA queries and/or Amgen customized queries) will also be summarized according to their categories and preferred term.

In addition, summaries of all adverse events and serious adverse events occurring in at least 5% of the subjects by preferred term in any treatment arm will be provided in descending order of frequency.

Summaries of adverse events and serious adverse events will be tabulated by system organ class, preferred term, and grade.

9.6.2.1 Adverse Events of Special Interest

This tentative list of adverse events of special interest has been based on the events of interest (EOI) identified for denosumab in the osteoporosis indication, and may be revised and changed later on to better reflect the OI population.

Event of Special Interest	**Search Strategy**	**Narrow or Broad Search?**
Hypocalcemia	Hypocalcemia AMQ	Narrow
Hypercalcemia	Hypercalcemia AMQ	Narrow
Positively adjudicated osteonecrosis of the jaw (ONJ)	Positively adjudicated cases in the database	NA
Hypersensitivity	Hypersensitivity SMQ	Narrow
Bacterial Cellulitis (skin infection)	Bacterial cellulitis AMQ with serious criteria of "hospitalization"	Narrow
Typical OI Femur Fractures (TOIFF)	Atypical femoral fractures AMQ	Narrow

In addition, Subject incidence for each adverse event of interest (EOI) will be presented by PT except for Positively adjudicated ONJ. Listing of Positively adjudicated ONJ and typical OI femur fractures (TOIFF) will be presented.

9.6.3 Laboratory Test Results

Actual values and changes from baseline in each parameter will be descriptively summarized at each visit. For serum calcium, phosphorus, and alkaline phosphatase (ALP), summary of the percent change from baseline also will be provided.

Shifts in laboratory parameters between baseline and the most extreme post baseline values will be assessed based on the CTCAE v4.03.

See details in Appendix A.

[redacted]

All laboratory analyses will be based on the safety analysis set and based on the German substudy **safety** analysis set. Subjects with missing data for a scheduled visit will not contribute to the tabulation for that time point (no imputation). Visit windows will be used for these summaries as described in Appendix C Analytical Windows

9.6.4 Vital Signs

Descriptive statistics of the actual values and changes from baseline in vital signs (heart rate, respiration rate, temperature) will be presented by visit for the SAS and based on the German substudy **safety** analysis set.

9.6.5 Physical Measurements

Physical measurements of height, weight and armspan will be summarized based on SAS.

9.6.6 Antibody Formation

Subjects receiving at least 1 dose of denosumab in 20170534 will be tested for antidenosumab antibodies. The numbers and percentages of subjects who tested positive (binding or neutralizing) for antidenosumab antibodies will be descriptively summarized.

9.6.7 Exposure to Investigational Product

Descriptive statistics (for number of injections) will be produced to describe the exposure to investigational product.

9.7 Other Analyses

9.7.1 Metaphyseal Index Z-Scores and Oral Hygiene

The subject incidence of the following safety events will be tabulated based on the SAS and German substudy **safety** analysis set.

- Metaphyseal index Z-score above age-appropriate normal range (ie, metaphyseal index Z-score > +2)
- Abnormal molar eruption of the first or second molars

Descriptive statistics (actual value, change from baseline, percent change from baseline) will be provided for the continuous endpoints of mandibular anatomical angles.

10. Changes From Protocol-specified Analyses

Removed the German substudy analysis set from section 6.3.4 as this definition was applicable to efficacy endpoints considering baseline and post baseline information for endpoint of interest. However to analyze the safety endpoints related German substudy the new definition is added as below in section 6.3.4,

German substudy safery analysis set - "The subset includes all subjects in the SAS who enroll in the German substudy."

Instead of Subject incidence of abnormal mandibular shaping, we will provide descriptive summary statistics for mandibular shaping parameters

11. Literature Citations / References

Ward K, Cowell CT and Little DG. Quantification of metaphyseal modeling in children treated with bisphosphonates. Bone 2005; 36: 999-1002

12. Data Not Covered by This Plan

Not applicable

13. Appendices

Appendix A Reference Values/Toxicity Grades

The Common Terminology Criteria for Adverse Events (CTCAE) are available at the following link:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix B Incomplete Dates and Missing Dates

The following data will be imputed using the following algorithm:

- **Concomitant Medications**

Imputation Rules for Partial or Missing Start Dates

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 Stop Dates

Initial imputation

- **If the month and year are present, impute the last day of that month.**
- **If only the year is present, impute December 31 of that year.**
- **If the stop date is entirely missing, assume the event or medication is ongoing.**

If the imputed stop date is before the start date, set stop date to missing.

If the imputed stop date is after the death date, impute as death date.

Appendix C Analytical Windows

Per protocol, all tests and procedures scheduled for Screening and Day 1 visit must be performed within 28 calendar days of the Study 20130173 End of Study visit. As specified in the protocol, all tests and procedures scheduled to occur at Months 3, 6, 9, 12, 15, 18, 21, and 24 should be performed within ± 7 days of the scheduled day. However, for analysis purposes the analysis visit windows defined below will be used to assign evaluations to the most appropriate nominal visit. Regardless of the width of the visit window, if more than 1 visits falls within the defined window, the results from visit closest to the target day will be used. If 2 evaluations are the same distance from the target day, the result from the later visit will be used. If the 2 evaluations have the same assessment dates, the first evaluation with the expected clinical planned event will be used.

Table C-1. Vital signs, Pregnancy Test (urine dipstick method), Physical Examination, Tanner Stage and Hematology, Urine calcium

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline*	1	Last evaluation prior to or on Study day 1
Month 3	92	Study Day 2 to 138
Month 6	183	Study Day 139 to 229
Month 9	275	Study Day 230 to 321
Month 12	366	Study Day 322 to 412
Month 15	458	Study Day 413 to 504
Month 18	549	Study Day 505 to 595
Month 21	641	Study Day 596 to 687
Month 24	732	After Study Day of 687

Table C-2. Chemistry

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline*	1	Last evaluation prior to or on Study day 1
Day 10	10	Study Day 2 to 20
Day 30	30	Study Day 21 to 61
Month 3	92	Study Day 62 to 97
Month 3 Day 10	102	Study Day 98 to 112
Month 3 Day 30	122	Study Day 113 to 153

Month 6	183	Study Day 154 to 188
Month 6 Day 10	193	Study Day 189 to 203
Month 6 Day 30	213	Study Day 204 to 244
Month 9	275	Study Day 245 to 321
Month 12	366	Study Day 322 to 412
Month 15	458	Study Day 413 to 504
Month 18	549	Study Day 505 to 595
Month 21	641	Study Day 596 to 687
Month 24	732	After Study Day of 687

Table C-4. Antidenosumab-antibody, Armspan

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline*	1	Last evaluation prior to or on Study day 1
Month 12	366	Study Day 2 to 549
Month 24	732	After Study Day of 549

Table C-5. DXA

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline*	1	Last evaluation prior to or on Study day 1
Month 6	183	Study Day 2 to 275

Month 12	366	Study Day **276** to 549
Month 24	732	**After Study Day of 549**

Table C-6. X-ray(AP knees)

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline*	1	Last evaluation prior to or on Study day 1
Month 6	183	Study Day 2 to 275
Month 12	366	Study Day 276 to 458
Month 18	549	Study Day 459 to 641
Month 24	732	After Study Day of 641

Table C-7. Dental X-ray (cephalogram and panoramic radiograph), Dental X-ray (molars)

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline*	1	Last evaluation prior to or on Study day 1
Month 6	183	Study Day of 2 to 275
Month 12	366	Study Day 276 to 458
Month 18	549	Study Day 459 to 641
Month 24	732	After Study Day of 641

Table C-8. Denosumab Administration, Dispensation of calcium and vitamin D, Alternative osteoporosis medications

Nominal Visit	Target Day	Window Definition (Study Day)
Day 1	1	Last evaluation prior to or on Study day 1
Month 3	92	Study Day 2 to 138
Month 6	183	Study Day 139 to 229
Month 9	275	Study Day 230 to 321
Month 12	366	Study Day 322 to 412
Month 15	458	Study Day 413 to 504
Month 18	549	Study Day 505 to 595
Month 21	641	Study Day 596 to 687
Month 24	732	After Study Day of 687

Table C-9. Visit window for Renal Laboratory Value

Nominal Visit	Target Day	Window Definition (Study Day)
Baseline	1	Study Day 1
Week 6	42	Study Day 2 to 49
Week 8	56	Study Day 50 to 63
Week 10	70	Study Day 64 to 77
Week 12	84	Study Day 78 to 109
Month 3 Week 6	134	Study Day 110 to 141
Month 3 Week 8	148	Study Day 142 to 155
Month 3 Week 10	162	Study Day 156 to 169
Month 3 Week 12	176	Study Day 170 to 201
Month 6 Week 6	225	Study Day 202 to 232
Month 6 Week 8	239	Study Day 233 to 246
Month 6 Week 10	253	Study Day 247 to 260
Month 6 Week 12	267	Study Day 261 to 292
Month 9 Week 6	317	Study Day 293 to 324
Month 9 Week 8	331	Study Day 325 to 338
Month 9 Week 10	345	Study Day 339 to 352
Month 9 Week 12	359	Study Day 353 to 384
Month 12 Week 6	408	Study Day 385 to 415
Month 12 Week 8	422	Study Day 416 to 429
Month 12 Week 10	436	Study Day 430 to 443
Month 12 Week 12	450	Study Day 444 to 475
Month 15 Week 6	500	Study Day 476 to 507
Month 15 Week 8	514	Study Day 508 to 521
Month 15 Week 10	528	Study Day 522 to 535
Month 15 Week 12	542	Study Day 536 to 567
Month 18 Week 6	591	Study Day 568 to 598
Month 18 Week 8	605	Study Day 599 to 612
Month 18 Week 10	619	Study Day 613 to 626
Month 18 Week 12	633	Study Day 627 to 683
Month 24	732	After Study Day of 683

* Baseline refers to Study 20170534 baseline as defined in this section 5.2.1 above