Statistical Analysis Plan

Protocol Title:	Long term Safety Follow up of Subjects With Giant Cell Tumor of Bone Treated With Denosumab in Study 20062004
Short Protocol Title:	Long term Safety Follow up of Subjects With Giant Cell Tumor of Bone Treated With Denosumab in Study 20062004
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	30 July 2017	Not applicable
Amendment 1 (v2.0)	11 August 2023	1. Used the new SAP template. 2. Incorporated updates in Protocol Amendment 2 (dated 23Aug2018) 3. Added/removed and updated some definitions in Section 5. 4. Clarified the summary/analysis methods for IPDs, disease progression or recurrence, and GCTB interventions in Sections 9.3, 9.5, and 9.6.9, respectively. 5. Detailed the summary/analysis methods for safety endpoints in Section 9.6.2.

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List of Abbreviations

Abbreviation	Explanation
AFF	atypical femur fracture
AE	adverse event
CI	confidence interval
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
EOS	end of study
EOT	end of treatment
GCTB	giant cell tumor of bone
ICF	informed consent form
IP	investigational product
IPD	Important protocol deviation
MedDRA	medical dictionary for regulatory activities
ONJ	osteonecrosis of the jaw
PD	progressive disease
PR	partial response
PT	preferred term
SAE	serious adverse event
SC	subcutaneous
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event

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 20140114, Denosumab dated **23 August 2018** .The scope of this plan includes the primary analysis that is planned for long-term safety follow-up of subjects with giant cell tumor of bone treated with denosumab in study 20062004 and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints/Estimands and Hypotheses

2.1 Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• Evaluate adverse events of interest in subjects with GCTB treated with denosumab in Study 20062004	• Rate of adverse events of interest in subjects with GCTB treated with denosumab in Study 20062004
Secondary	
• Evaluate treatment-emergent adverse events for subjects who are receiving denosumab	• Rate of treatment-emergent adverse events for subjects who are receiving denosumab
• Evaluate serious adverse events for all subjects	• Rate of serious adverse events for all subjects
• Summarize the rate of disease progression or recurrence of GCTB for all subjects	• Rate of disease progression or recurrence of GCTB for all subjects
• Summarize the use of GCTB interventions for all subjects	• Rate of GCTB interventions for all subjects

Estimand(s) for Primary Objective(s)

Not Applicable

Estimand(s) for Secondary Objective(s)

Not Applicable

Exploratory
Not Applicable

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

This prospective study will provide long-term safety follow up for subjects who complete Study 20062004 and consent to enroll in Study 20140114. The subject's follow up begins after signing the informed consent form (ICF) and continues through the earliest date of: 5 years after **the last subject enrolled signs** the ICF, death, withdrawal of consent, or lost to follow up.

Study assessments are to be completed every 6 months (± 30 days). **End of study (EOS) visits for all patients will be at 5 years**.

There will be 2 cohorts in this study:

Cohort A - subjects who were receiving denosumab at the conclusion of Study 20062004 can continue receiving denosumab at the current dose and schedule (Q4W) at the investigator's discretion. **Follow-up study visits will be performed in clinic every 6 months (± 30 days) while receiving denosumab. Cohort A subjects on investigational product will have an EOS visit conducted 30 days following the last dose of investigational product (end of treatment [EOT] visit) if receiving investigational product at the 5 year time point. Subjects who discontinue denosumab will have an EOT in-person clinic visit approximately 30 days (± 8 days) after the last dose of denosumab. Thereafter, they will enter the long-term safety follow-up and will be monitored as per Cohort B requirements.**

Cohort B - subjects who completed denosumab treatment in 20062004 and were in the safety follow-up at the conclusion of 20062004 will continue in long-term safety follow-up in this study. Follow-up study visits will be done every 6 months (± 30 days) either via telephone or in-person clinic visit.

Retreatment with denosumab (120 mg subcutaneous [SC] **on days 1, 8, 15, and 28, then every 4 weeks subsequently**) is allowed for subjects who previously demonstrated a response to denosumab and have experienced disease recurrence while in long-term safety follow-up at the investigator's discretion.

For Cohorts A and B - laboratory assessments are not mandated by the study and will be performed at the investigator's discretion as part of the standard of care or as clinically indicated.

At each follow-up study visit, subjects will be assessed (for in-person clinic visit) or asked (for visit via telephone) for signs and symptoms of the following events of interest: osteonecrosis of the jaw (ONJ), malignancy (including malignancy in GCTB), atypical femoral fracture (AFF), hypocalcemia **(assessed per Common Terminology Criteria for Adverse Events [CTCAE] criteria)**, hypercalcemia following treatment discontinuation **(assessed by CTCAE criteria)**, and pregnancy and lactation (if occurring on treatment or within 5 months of last dose of denosumab). Additionally, all treatment emergent adverse events and serious adverse events will be collected

3.2 Sample Size

The number of subjects in this study will be determined by the number of subjects completing Study 20062004, and who are willing to enroll in this study for long-term safety follow-up. It is estimated that this will be approximately 100 to 300 subjects.

For the expected sample size of 100 to 300 subjects, the 95% confidence interval (CI) based on exact method for the incidence rate of a particular adverse event is calculated below **Table 1** if none of the subjects report a particular adverse event then a true incidence rate of more than 3.6% for 100 subjects and 1.2% for 300 subjects is unlikely for that particular adverse event.

Table 1. Estimated 95% Confidence Interval for Example Adverse Event of Interest Incidence Rate

Number of Subjects Reporting Adverse Event	Adverse Event Incidence Rate	
	Estimate (%)	95% CI (%)
0/100	0	(0.0, 3.6)
1/100	1	(0.0, 5.4)
5/100	5	(1.6, 11.3)
10/100	10	(4.9, 17.6)
0/200	0	(0.0, 1.8)
2/200	1	(0.1, 3.6)
10/200	5	(2.4, 9.0)
20/200	10	(6.2, 15.0)
0/300	0	(0.0, 1.2)
3/300	1	(0.2, 2.9)
15/300	5	(2.8, 8.1)
30/300	10	(6.8, 14.0)

CI = confidence interval

3.3 Adaptive Design

Not Applicable

4. Covariates and Subgroups

4.1 Planned Covariates

Not applicable

4.2 Subgroups

Treatment-emergent adverse events, overall serious adverse events and adverse events of interest will be summarized using adolescent analysis set.

5. Definitions

- **Investigational Product (IP)**

  IP for this study refers to denosumab.

- **Study Day 1**

  The date on which the subject signs the informed consent for this study.

- **Study Day**

  The number of days from study day 1 to a date of interest, inclusive: Study day = (date of interest – study day 1) + 1.

- **Treatment Emergent Adverse Event (TEAE)**

  An adverse event is considered as treatment emergent if the adverse event occurs during the time period from the first dose of IP in this study through last dose of IP plus **30** days. For subject without retreatment, this is **30** days after the last dose of IP in the treatment phase, for subject with retreatment(s), this is **30** days after the last dose of IP in the last retreatment phase.

- **Original First Dose of IP**

  The first dose of IP taken by the subject in study **20062004**

- **First Dose of IP in Study 20140114**

  The first dose of IP after the subject enrolled on study 20140114.

- **Exposed to IP in Study 20140114**

  A subject is considered as exposed to IP if the subject has received one or more doses of IP in study 20140114.

- **IP Exposure Time in Study 20140114**

  IP exposure is considered from the first dose of IP to the last dose of IP plus 28 days **in study 20140114**. If subject has retreatment(s), IP exposure will be the total exposure time over each treatment phase(s).

- **End of Study (EOS) Date for an Individual Subject**

  The EOS date is recorded on the End of Study page of the Case Report Form (CRF) for an enrolled subject.

- **Gap Period**

  Gap period is defined as after the end of study 20062004 to before the study Day 1 of study 20140114.

- **Events of Interest**

  Adverse events of interest **include:**

1. Osteonecrosis of the Jaw
2. Malignancy, including malignancy in GCTB
3. Atypical femur fracture
4. Hypocalcemia (assessed per Common Terminology Criteria for Adverse Events [CTCAE] criteria)
5. Hypercalcemia following treatment discontinuation (assessed by CTCAE criteria)
6. pregnancy and lactation (if occurring on treatment or within 5 months of last dose of denosumab)

- **Time to osteonecrosis of the Jaw (ONJ)**
  Time to ONJ is defined as the time interval (in days) from the original first dose of IP to the date of first adverse event of adjudicated positive ONJ. For Kaplan-Meier estimates, s**ubjects without adjudicated positive ONJ will be censored at EOS date of study 20140114 (for subjects entered into study 20140114), or censored at the latest date of end of initial treatment phase, end of retreatment phase, and end of safety follow-up phase of Study 20062004 (for subject who didn't enroll in study 20140114).**

- **Progressive Disease (PD)**
  It is defined as the response of progressive disease, locally recurrent disease or distant recurrence as captured in the Disease Status page of the CRF.

- **Disease Progression or Recurrence**
  It is defined as the best post-baseline response of PD in study 20140114 without any post-baseline complete response (CR) /partial response (PR) /stable disease(SD) or a post-baseline response of PD following a post-baseline CR/PR/SD.

6. Analysis Sets

6.1 Full Analysis Set

Full analysis set includes all enrolled subjects (from 20062004) who have provided informed consent and have a non-missing enrollment date in this study.

6.1.1 Adolescent Analysis Set

Adolescent analysis set includes all enrolled subjects in this study who were younger than 18 years when enrolled in 20062004.

6.2 Safety Analysis Set

In this study, safety analysis will be conducted in the Full Analysis Set and Adolescent Analysis Set. Safety Analysis Set is not defined separately then.

6.3 Per Protocol Set(s)

Not Applicable

6.4 Health-related Quality-of-Life or Health Economics Analyses Set(s)

Not Applicable

6.5 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

Not Applicable

6.6 Interim Analyses Set(s)

There is no interim analysis planned for this study.

6.7 Study-specific Analysis Set(s)

Not Applicable

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Not Applicable

7.2 Primary Analysis

The primary analysis is the only planned analysis for this study. It will occur upon completion of the study when all subjects have had the opportunity to complete 5 years of follow-up in this study.

7.3 Final Analysis

Not Applicable

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 and ARGUS database

8.3 Handling of Missing and Incomplete Data

Subjects may have missing data points for a variety of reasons. In general, data may be missing due to subject's early withdrawal from study, a missed visit, or non-evaluability of an endpoint at a particular point in time. The procedures outlined in **Appendix G** describing what will be done when data are missing .

8.4 Detection of Bias

Not Applicable

8.5 Outliers

Descriptive statistics will be used to identify outliers in applicable key variables for analysis. For continuous variables, the univariate analyses will be conducted and scatter plots will be generated to identify outliers. For discrete variables, frequency summary will be examined to identify questionable values.

Outliers due to data entry error will be corrected in the database before the database freeze. Outliers that are not due to data entry error will be included in the primary analysis, unless there is sufficient clinical justification obtained prior to analysis snapshot and database lock to exclude them. The validity of any questionable values or outliers will be confirmed. No valid measurement may be excluded from descriptive or inferential analyses

8.6 Distributional Characteristics

No assumption will be checked. Primary analyses are descriptive in nature.

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

The statistical analysis in this long-term safety follow up study will be descriptive in nature and no hypothesis testing will be performed. The analysis will be based on the full

analysis set defined in Section 6. In general, data summaries will be presented by the condition whether subjects were exposed to IP during 20140114. Categorical outcomes will be summarized by the number and percentage of subjects in each category. Continuous outcomes will be summarized by the number of non missing values, mean, standard deviation, median, lower and upper quartiles and minimum and maximum values.

9.2 Subject Accountability

For the full analysis set and adolescent analysis set, the numbers and percentages of subjects who discontinued from investigational product by reason will be provided. Similarly, the numbers and percentages of subjects who discontinued the study by reason will be summarized.

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.

The number and percentage of subjects with IPD and covid-19 related IPD/PD will be summarized by protocol deviation category. IPDs will also be listed.

9.4 Demographic and Baseline Characteristics

The following descriptive summaries of the demographic and baseline characteristics will be produced for the full analysis set:

- Subjects enrollment by country and investigator
- Subjects disposition includes discontinued IP/study, and reason for IP/study discontinuation
- Summary of demographics will include: age, sex, race, and geriatric age group (if applicable).
- Summary of medical history by preferred term.
- Summary of baseline disease classification and status.

In addition, subject disposition, demographics, and baseline disease classification and status will also be summarized for the adolescent analysis set.

9.5 Efficacy Analyses

For the full analysis set and adolescent analysis set, the rate of disease progression or recurrence of GCTB and GCTB disease status with best

response will be summarized by exposed to IP in 20140114 and not

exposed to IP in 20140114.

9.5.1 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)

Not Applicable

9.5.2 Analyses of Secondary Efficacy Endpoint(s)/Estimand(s)

Not Applicable

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)/Estimand(s)

Not Applicable

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Safety Endpoints		**Primary Summary and Analysis Method**
Primary	• Rate of adverse events of interest in subjects with GCTB treated with denosumab in Study 20062004	• Subject incidence of adverse events of interest will be summarized. Subject-year adjusted rate of certain adverse events of interest will also be summarized. The detailed summary and analysis methods are specified in Section 9.6.2 below.

9.6.2 Adverse Events

The current Medical Dictionary for Regulatory Activities (MedDRA) version will be used to code all adverse events (AEs) and adverse events of interest to a system organ class **(SOC)** and a preferred term **(PT)**. For AE tables, all subjects in full analysis set will be analyzed and separately summarized in two groups, namely, subjects exposed to IP in 20140114 and subjects never exposed to IP in 20140114.

For treatment-emergent adverse events, subject incidence will be tabulated **for the categories listed below** by SOC, **high level term** and PT; by SOC and PT; and by PT only, respectively.

- All treatment-emergent adverse events

- **Treatment-emergent serious adverse events**
- **Treatment-emergent fatal adverse events**
- **CTCAE grade 3, 4, or 5 treatment-emergent adverse events**
- **Treatment-emergent adverse events leading to IP discontinuation**

Subject incidence of IP related treatment-emergent adverse events will be summarized by PT only. Subject-year adjusted event rate of all treatment-emergent adverse events and treatment-emergent serious adverse events will also be produced.
For all SAEs and SAEs in follow up period, subject incidence will be tabulated by SOC and PT, and by PT only. Subject-year adjusted event rate for all SAEs will be produced. The SAEs collected in study 20140114 that started during the gap period will also be listed.

For adverse event of interest, i.e., **adjudicated positive** osteonecrosis of the jaw (ONJ), malignancy (including malignancy in GCTB), **adjudicated positive** atypical femoral fracture (AFF), hypocalcemia, and hypercalcemia following treatment discontinuation, subject incidence will be tabulated by PT. The proportion of subjects with adverse events of interest will be estimated with 95% CI based on an exact method i.e. Clopper-Pearson method for proportion and CI calculations. The adjudicated positive ONJ, malignancy and adjudicated positive AFF collected in study 20140114 that started during the gap period will also be listed.

In addition, for adjudicated positive ONJ, malignancy (including malignancy in GCTB), **and adjudicated positive AFF**, the safety analysis will also be conducted based on combined data from studies 20062004 and 20140114 by the enrollment cohorts in study 20062004.

- **Osteonecrosis of the Jaw**

Combining data from studies 20062004 and 20140114, the subject incidence of adjudicated positive ONJ will be summarized. Subject-year adjusted rate of adjudicated positive ONJ starting from original first dose of IP in 20062004 will be tabulated by PT and by time period. Time to first positive ONJ will be analyzed using Kaplan-Meier estimates with 95% CI. A KM plot for time to first adjudicated positive ONJ will be provided for combined cohorts.

- **Malignancy**

The incidence of malignancy in GCTB will be summarized to compare with the historical control rates based on the published literature. Combining data from studies 20062004 and 20140114, the proportion of subjects who have malignancy (including malignancy in GCTB) will be summarized. Subject-year adjusted rate of malignancy starting from original first dose of IP in 20062004 will be tabulated by PT and by time period.

- **Atypical Femur Fracture**

Combing data from studies 20062004 and 20140114, subject incidence of adjudicated positive AFF will be summarized. Listing of adjudicated positive AFF events will be provided.

Safety analysis will be repeated for adolescent subjects as applicable. For subjects in the adolescent analysis set of study 20140114, subject incidence of treatment-emergent adverse events and adverse events of interest will be summarized. Subject listing of adverse events (including treatment-emergent adverse events, all serious adverse events, and adverse events of interest) will be provided. Combining data from studies 20062004 and 20140114, subject incidence of adjudicated position ONJ, malignancy, and adjudicated positive AFF will be tabulated for adolescent subjects in the safety analysis set of study 20062004.

9.6.3 Laboratory Test Results

Not Applicable.

9.6.4 Vital Signs

Not Applicable

9.6.5 Physical Measurements

Not Applicable

9.6.6 Electrocardiogram

Not Applicable

9.6.7 Antibody Formation

Not Applicable

9.6.8 Exposure to Investigational Product

Administration dates and doses of IP will be collected and cumulative IP exposure will be summarized using descriptive statistics **for study 20140114**. Similar analysis for doses of IP will be performed **for studies 20062004 and 20140114 combined** starting from the original first IP dose in Study 20062004.

9.6.9 Exposure to Non-investigational Product

Embolization, radiotherapy, interferon, chemotherapy or other therapeutic agents, and surgery for GCTB since last contact were collected on CRF page of GCTB Intervention. For full analysis set and adolescent analysis set, rate of those GCTB interventions (Yes/No) will be summarized by exposed to IP and not exposed to IP in study 20140114.

9.6.10 Exposure to Other Protocol-required Therapy

Not Applicable

9.6.11 Exposure to Concomitant Medication

Prior concomitant medication and concurrent concomitant medication will be summarized by preferred term coded by the World Health Organization Drug (WHO DRUG) dictionary for the full analysis set.

9.7 Other Analyses

Not Applicable

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Not Applicable

9.7.2 Analyses of Clinical Outcome Assessments

Not Applicable

9.7.3 Analyses of Health Economic Endpoints

Not Applicable

9.7.4 Analyses of Biomarker Endpoints

Not Applicable

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

Denosumab Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

XGEVA® [package insert]. Thousand Oaks, CA: Amgen, Inc.; March 2016.

12. Prioritization of Analyses

Not Applicable

13. Data Not Covered by This Plan

Not Applicable

14. Appendices

Appendix A. Reference Values/Toxicity Grades

Not Applicable

Appendix B. Concomitant Medications

Not Applicable

Appendix C. Clinical Outcome Assessment Forms/Instruments

Not Applicable

Appendix D. Health Economic Forms/Instruments

Not Applicable

Appendix E. Details of PK or PK/PD Methods for Modeling

Not Applicable

Appendix F. Analytical Windows

Not Applicable

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

Imputation Rules for Partial or Missing Start/Stop Dates

Incomplete event start dates and concomitant medications start or stop dates will be imputed as described in the table below. If the start date is missing, assume the event or medication started before enrollment; if the stop date and the flag for medication continuing are both missing for an on-study event or medication, assume the event or medication stopped after the end of study date. Partial dates will be listed as is on the listings.

14.1 Table 2. Imputation Rules for Incomplete Dates

	Missing	Imputation	Exception
Start date (AE, concomitant medication)	Day	01	Default to study day 1 if an event starts the same year and month as study day 1
	Day / Month	01JAN	Default to study day 1 if an event started the same year as study day 1
Stop date (concomitant medication only)	Day	Last day of the month	Default to the End of Study (EOS) date if the concomitant medication stopped the same year and month as the EOS date
	Day / Month	**31DEC**	Default to the EOS date if the concomitant medication stopped the same year as the EOS date