Statistical Analysis Plan

Protocol Title:	Open-Label Access Protocol of Denosumab for Subjects with Advanced Cancer
Short Protocol Title:	
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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AE	Adverse event
AFF	**Atypical femoral fracture**
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
EDC	Electronic data capture
GSO-DM	**Global Study Operations-Data Management**
IP	Investigational product
IPD	Important protocol deviation
IVRS	Interactive voice response system
MedDRA	Medical Dictionary for Regulatory Activities
mg/dL	Milligrams per deciliter
mmol/L	Millimole per liter
ONJ	Osteonecrosis of the jaw
Q4W	Every 4 weeks
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	**System organ class**

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 20110113, Denosumab dated **22 February 2013.** The scope of this plan includes the final 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 facilitate the access of denosumab for subjects with advanced cancer who have participated in a denosumab phase 3 study until denosumab is approved and available for sale.	
Secondary Safety	
• To further assess the safety of denosumab for subjects who have participated in open label extensions of a denosumab advanced cancer phase 3 study.	• Subject incidence of treatment-emergent adverse events (AEs) • Subject incidence of anti-denosumab antibody (binding and neutralizing) formation

2.2 Hypotheses and/or Estimations

A formal statistical hypothesis will not be tested or estimated.

3. Study Overview

3.1 Study Design

This is an open-label, single-arm access protocol for subjects with advanced cancer. Subjects will be offered open-label denosumab at a dose of 120 mg SC Q4W until denosumab is approved and available for sale. Amgen may end this study prior to denosumab being approved and available for sale if another mechanism is identified to provide denosumab to ongoing subjects, or as otherwise stated in Section 12.1 of the protocol 20110113.

Severe hypocalcemia can occur in subjects receiving denosumab. Calcium levels should be monitored as part of routine clinical practice. It is strongly recommended that all subjects receive daily supplements of at least 500 mg calcium and at least 400 IU of

vitamin D, unless documented hypercalcemia (albumin-adjusted serum calcium > 2.9 mmol/L [11.5 mg/dL] or ionized calcium > 1.5 mmol/L [6.0 mg/dL]) develops on study. Due to differences in regional availability, a dosage form of Vitamin D that gives an equivalent of at least 400 IU daily may be given.

Osteonecrosis of the jaw (ONJ) can occur in subjects receiving denosumab. Subjects should be monitored for ONJ as part of routine clinical practice. Subjects should be instructed to maintain good oral hygiene, and avoid invasive dental procedures, if possible.

3.2 Sample Size

The statistical reporting of the study endpoints will be entirely descriptive **(summary statistics),** with no formal statistical hypothesis tested or estimated. The number of subjects will be determined by the number of subjects who qualify for the protocol. It is estimated that up to approximately 400 subjects will participate in this study.

3.3 Adaptive Design

Not applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

Not applicable.

4.2 Subgroups

Not applicable.

5. Definitions

Basic Definitions

- Investigational Product (IP)

IP for this study refers to denosumab.

- IVRS

An IVRS (interactive voice response system) will be used in this study to assign eligible subjects to IP as well as to manage IP supply at the site and track subject study termination data.

Study Points of Reference

- Study Day 1

The date of the first IP administration after enrollment or the date of enrollment for subjects who are not administrated any dose of IP during this study.

- Study Day

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

Study Dates

- Informed Consent Date

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

- Enrollment Date

The enrollment date is the date on which a subject is registered as enrolled in the study **through** the IVRS **system**.

- First Dose Date

The first dose date is the date on which a subject is administered the first dose of the IP **in this study.**

- Last Dose Date

The last dose date is the date on which a subject is administered the final dose of the IP **in this study.**

- End of Study Date for a Subject

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

Study Time Intervals

- Screening period

The screening period for a subject is defined as the time from the informed consent date to the day of enrollment.

- On-Study Period

For **the final analysis**, the on-study period for an enrolled subject is defined as the time from the day of enrollment to the end of study date on the CRF.

Subject Dispositions

- Enrolled

Individuals are considered enrolled if they have **a non-missing date of enrollment.** Enrolled individuals are referred to as "subjects".

- On-Study

Subjects are considered on-study during the period between the date of enrollment and the end of study date on the CRF.

- Exposed to Investigational Product

Subjects are considered as exposed to IP if they have received one or more non-zero doses of IP **in this study**.

Derived Variables

- Subject Incidence Rate

The subject incidence rate for a given event is defined as the number of subjects with one or more reported occurrence of the event divided by the number of subjects who have the opportunity to report the event.

- Subject Age at Study Entry

Age at study entry is defined as the number of whole years from a subject's birth date to the enrollment date as calculated in the **Electronic Data Capture (EDC)** RAVE database.

- Subject-years on Study for Safety **Analysis**

The sum of days on study (the end of study date on the CRF – first dose date +1) for all subjects **in the safety analysis set** divided by 365.25.

- **Subject-year** Adjusted Adverse Event Rate

The number of AEs reported in the given time period divided by total subject-years on study during the period**.**

6. Analysis Sets

Subjects will be excluded from all analyses and all data subsets if properly documented informed consent was not obtained. These subjects will be **identified, and** safety data for these subjects will be provided separately in the clinical study report.

6.1 Full Analysis Set

This subset includes all subjects who are enrolled in this study, except for data collected from subjects without properly documented informed consent as described above.

6.2 Safety Analysis Set

This subset includes all subjects who **are enrolled and** received at least one dose of IP **in this study**, except for data collected from subjects without properly documented informed consent as described above.

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)

Not applicable.

7. Planned Analyses

Only final analysis will be conducted.

7.1 Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study.

7.2 Primary Analysis

No primary analysis is planned for this study.

7.3 Final Analysis

Final analysis will be conducted after all subjects complete/discontinue 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. Any questionable values or situations will be reported to Clinical Data Management for review or confirmation.

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 **EDC** RAVE 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 below describing what will be done when data are missing may be refined during the review of the data. Incomplete AE start dates will be imputed as described in Table 1. If the start date is **completely** missing, **default to study day 1 if the indicator of "Did event start before the first dose of investigational product" is checked as "No".** Partial dates will be listed as is on the listings.

Table 1. Imputation Rules for Incomplete Dates

	Missing	Imputation	Exception
AE start date	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

If a death date is incomplete and missing only the day field, the partial death date (also end of IP or end of study date if death is the reason **for discontinuation**) will be imputed as follows: if the latest assessment for this subject is before the month of the death, it will be imputed as the first day of the month; if the latest assessment is within the same month as the death, it will be imputed using this latest assessment date.

8.4 Detection of Bias

Not applicable.

8.5 Outliers

Not applicable.

8.6 Distributional Characteristics

Not applicable.

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.

9. Statistical Methods of Analysis

9.1 General Considerations

The statistical analysis in this study will be entirely descriptive. Continuous variables will be summarized using descriptive statistics, which includes the number of non-missing observations (n), the mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum. The minimum and maximum will be reported using the same precision as the original measurement. The mean, median, other selected percentiles and standard deviation will be reported to one decimal place more than the precision of the original measurement. Descriptive statistics provided for categorical outcomes will include the frequency and percentage.

The analyses of safety endpoints will be based on the safety analysis set defined in **Section 6.2.**

9.2 Subject Accountability

For all enrolled subjects, the number and percentage achieving the planned assessments listed below will be tabulated:

- Subject enrollment by **geographic region,** country and site
- Number and percentage exposed to IP
- Number and percentage enrolled, but not exposed to IP
- Number and percentage discontinuing IP administration by reason
- Number and percentage of subjects discontinuing study by reason
- Important on-study protocol deviations

Listings will be provided for important protocol deviations for all enrolled subjects.

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. The final IPD list is used to produce the Summary of IPDs table and the List of Subjects with IPDs.

9.4 Demographic and Baseline Characteristics

Descriptive statistics will be tabulated for demographics as listed below on all enrolled subjects in this study.

- Gender
- Age at study entry (year)
- Age group **(18 - 64 years, 65 - 74 years, 75 - 84 years, ≥ 85 years)**
- Ethnic group/Race

9.5 Efficacy Analyses

Not applicable.

9.5.1 Analyses of Primary Efficacy Endpoint(s)

Not applicable.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Not applicable.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

Not applicable.

9.6 Safety Analyses

9.6.1 Analyses of Safety Endpoints

Safety analyses in this study will include assessments of treatment-emergent AEs, AEs of interest, and immunogenic response. The following sections summarize the analysis methods for these safety endpoints. The safety **analysis set** defined in **Section 6.2** will be **used** in these analyses.
In addition, IP exposure **will also be summarized.**

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version **20** or later will be used to code all AEs. **Treatment-emergent AEs are events with an onset after the administration of the first dose of IP in this study.** Based on the AE summary

instructions, an AE that exists prior to the administration of IP and gets worse after the first dose of IP will be included as a treatment-emergent AE.

The analysis of AEs will be descriptive. **For treatment-emergent AEs, serious AEs, CTCAE grades 3, 4, and 5 AEs, fatal AEs, AEs leading to IP discontinuation or study discontinuation, and serious AEs leading to IP discontinuation or study discontinuation** listed in **Table 2**, subject incidence will be summarized by system organ class (SOC) and preferred term**, and by preferred term only. Subject incidence for treatment-emergent AEs by SOC, preferred term and worst grade will be tabulated.** Subject-year adjusted adverse event rates will be summarized for **treatment-emergent** AEs, serious AEs, and CTCAE grades 3, 4, and 5 AEs **by SOC and preferred term, and by preferred term only.** Summary tables for investigator determined IP related **treatment-emergent** AEs will be provided **by preferred term only.** In addition, subject incidence for **treatment-emergent** AEs and serious AEs by SOC and preferred term will be summarized by time period (e.g., 0 - 6 months, >6 – 12 months, >12 months).

Events of interest (EOIs), including AEs of hypocalcaemia, infections **and infestations,** ONJ**, osteonecrosis excluding the jaw,** new primary malignancy, cardiac/vascular disorders**, atypical femur fracture (AFF), musculoskeletal pain,** and AEs potentially associated with hypersensitivity will be summarized. **Subject incidence of treatment-emergent AEs and SAEs of these EOIs will be tabulated at the EOI level and preferred term level.**

Osteonecrosis of the Jaw Adjudication

All subjects with an oral AE suspicious of ONJ should be examined by a dentist or other qualified oral specialist (e.g., oral surgeon). Potential events of ONJ are identified by: **a) obtaining the available information from investigators on pre-specified oral event terms including those specifically reported as ONJ; b) regular assessment of the clinical trial database to detect maxillofacial events which might be indicative of ONJ; c) review and assessment of all these events by an independent adjudication committee. All adjudicated positive ONJ events with triggering adverse events having onset after the administration of the first dose of IP in this study (i.e., the treatment-emergent adjudicated positive ONJ) will be included in the analysis of EOIs. Subject-year adjusted rate of treatment-emergent adjudicated**

positive ONJ by time period (e.g., 0 – 12 months, >12 – 24 months, >24 – 36 months, >36 months) will also be presented.

Atypical Femoral Fracture Adjudication

All subjects presenting with new or unusual thigh, hip, or groin pain should be evaluated for a suspected AE of AFF. AEs reported as AFF as well as AEs identified by Amgen as potentially representing AFF will be reviewed by an independent adjudication committee of experts to determine whether the pre-defined criteria for AFF are met. Amgen will request the investigating site to provide all available source documents surrounding that event to be reviewed by the adjudication committee. The treatment-emergent adjudicated positive AFF events will be included in the analysis of EOIs.

Table 2. Safety Endpoints for Treatment-emergent Adverse Events

Parameter	Time Point
Subject incidence of the following treatment-emergent AEs: All AEs All investigator determined IP related AEs CTCAE Grade 3, 4, and 5 AEs Serious AEs Fatal AEs AEs leading to IP discontinuation AEs leading to study discontinuation Serious AEs leading to IP discontinuation Serious AEs leading to study discontinuation	Study day 1 through the end of study

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

Immunogenic response will be described by tabulating the numbers and percentages of subjects who tested positive (binding, neutralizing) for anti-denosumab antibodies in subjects receiving at least one dose of IP. If a subject tests positive for neutralizing antibodies against denosumab, the relationship between the presence of neutralizing antibodies and AEs will be evaluated.

Table 3. Anti-denosumab Antibody

Parameter	Time Point
Anti-denosumab Antibody (binding/neutralizing)	End of study visit

9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to IP. The number of **months** on study, number of doses received, and cumulative IP exposure will be summarized.

9.6.9 Exposure to Other Protocol-specified Treatment

Not applicable.

9.6.10 Exposure to Concomitant Medication

Not applicable.

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

None.

12. Prioritization of Analyses

None.

13. Data Not Covered by This Plan

None.

14. Appendices

Appendix A. Reference Values/Toxicity Grades

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

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.