STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study of Denosumab as Adjuvant Treatment for Women with Early-Stage Breast Cancer at High Risk of Recurrence (D-CARE)

Protocol Number 20060359

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Table of Abbreviations

Abbreviation	Definition
AE	adverse event
AFF	atypical femoral fracture
CRF	case report form
CTCAE	common terminology criteria for adverse Events
EOI	event of interest
EOTP	end of treatment phase
IP	investigational product
LTFU	long-term follow-up
MedDRA	medical dictionary for regulatory activities
ONJ	osteonecrosis of the jaw
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan

1. Introduction

The primary analysis for Amgen protocol 20060359, entitled "A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study of Denosumab as Adjuvant Treatment for Women with Early-Stage Breast Cancer at High Risk of Recurrence (D-CARE)", was performed based on data collected through the primary analysis data cut-off date, 31 August 2017, according to the statistical analysis plan (SAP) version 3.0 dated on 15 November 2017. According to the protocol amendment 4 dated on 17 October 2016, all subjects on study at the primary analysis data cut-off date completed the end of treatment phase (EOTP) visit and entered in the long-term follow-up (LTFU) phase after the primary analysis data cut-off date. In early 2018, Amgen decided to close the study in April 2018 and carry out the final analysis, specifically the final database lock was planned on 12 April 2018. This addendum to SAP version 3.0 describes the data analysis plan for conducting the final analysis. The efficacy and safety data collected through the final database lock are included in this analysis.

2. Study Endpoints

Per the study design (please refer to protocol amendment 4 Section 7.1.4.2 and SAP version 3.0 Section 3.1), following the primary analysis data cut-off date, all subjects should complete the EOTP visit and would be followed by clinic visit or telephone contact every 6 months (± 1 month) for survival only. Study endpoints to be analyzed in the final analysis are listed as follows.

2.1 Efficacy Endpoint

Endpoint	Analysis Time Period
Overall survival (determined by the time from randomization to death from any cause)	Randomization through the final database lock

2.2 Safety Endpoints

Parameter	Analysis Time Period
Treatment-emergent adverse events (AEs): All AEs Serious AEs (SAEs) Fatal AEs CTCAE Grade 3, 4, and 5 AEs AEs leading to investigational product (IP) discontinuation AEs leading to study discontinuation New AEs reported after the primary analysis Changed AEs with changes in reported AE term and/or serious flag after the primary analysis Adverse events of interest (EOIs)	Unless otherwise specified, the analysis time period is from study day 1 through 30 days after the last dose of IP or the final database lock, whichever is earlier

Note: The Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 or higher will be used.

3. Statistical Methods of Analysis

This section summarizes the analysis methods for the final analysis.

3.1 Subject Accountability

For all randomized subjects, the number and percentage achieving the planned assessments listed below will be tabulated by treatment arm:

- Subjects who enrolled study, subjects who discontinued study by their reasons for study discontinuation, subjects with complete follow-up (ie, dead, or known to be alive at the end of the study)
- Important protocol deviations

In addition, listings will be provided for important protocol deviations and protocol inclusion/exclusion deviations.

3.2 Efficacy Analyses

Overall survival will be analyzed using the full analysis set (please refer to SAP version 3.0 Section 6.1.1 for the definition of full analysis set).

Kaplan-Meier estimates of the survival functions will be graphically displayed for each treatment group. Kaplan-Meier quartiles (25^{th} percentile and median) with 2-sided 95% confidence intervals will be calculated if applicable. In addition, overall survival time will be summarized via displaying number of subjects at risk, the percent of subjects that died, and Kaplan-Meier survival rates with 2-sided 95% confidence intervals at year 1, year 2, year 3, year 4, and year 5.

A log-rank test stratified by the randomization stratification factors (please refer to SAP version 3.0 Section 3.1) will be used to compare overall survival of the two treatment groups. The hazard ratio of denosumab compared with placebo and its corresponding 2-sided 95% confidence interval will be estimated using a Cox proportional hazards model with treatment group as the independent variable and stratified by the randomization stratification factors.

3.3 Safety Analyses

In safety analyses, the safety analysis set (please refer to SAP version 3.0 Section 6.1.3 for its definition) will be used, and no statistical testing is planned.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or higher. As defined in the SAP version 3.0 Section 9.4.1, treatment-emergent AEs are events occurred during the time period from the first dose date (AEs are excluded if the indicator of "Did event start before the first dose of investigational product?" is checked as "Yes" on Adverse Events Summary CRF pages) through 30 days after the last dose of IP. Based on the AEs summary instructions, an AE that exists prior to the administration of IP and gets worse during the time period defined above will be included as a treatment-emergent AE. Unless otherwise specified, all AE related analyses are based on treatment-emergent AEs.

For all AEs, SAEs, grade ≥ 3 (ie, CTCAE grade 3, 4, and 5) AEs, fatal AEs, AEs leading to discontinuation of IP or study, as listed in Section 2.2, subject incidence will be summarized. Subject incidence by system organ class, high level term and preferred term (PT) will be tabulated for all AEs, SAEs, and fatal AEs. In addition, listings will be provided for new AEs reported after the primary analysis, and the changed AEs with changes in reported AE term and/or serious flag after the primary analysis.

For EOIs, including AEs of hypocalcaemia, osteonecrosis of the jaw (ONJ), new primary malignancy, atypical femur fracture (AFF), cardiac/vascular disorders, infections and infestations, AEs potentially associated with hypersensitivity, osteonecrosis excluding the jaw, musculoskeletal pain, and hypercalcemia occurred after 30 days following discontinuation of IP, subject incidence of AEs and SAEs will be tabulated.

- All adjudicated positive ONJ events with triggering AEs having onset dates up to the final database lock will be included in the analysis. The proportion of subjects experiencing adjudicated positive ONJ will be summarized. Subject-year adjusted incidence rate of adjudicated positive ONJ by incremental time period (0-12 months, >12 - 24 months, >24 - 36 months, >36 - 48 months, >48 months) will be presented. A Kaplan-Meier plot for time to first adjudicated positive ONJ will be provided.
- AEs that are adjudicated as positive for AFF and have onset dates up to the final database lock will be included in the analysis. The proportion of subjects experiencing adjudicated positive AFF will be summarized. Subject-year adjusted incidence rate of adjudicated positive AFF by incremental time period (0-12 months, >12 - 24 months, >24 - 36 months, >36 - 48 months, >48 months) will be presented. A Kaplan-Meier plot for time to first adjudicated positive AFF will be provided.