Protocol Title: 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)

Denosumab (AMG 162)

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Investigator's Agreement

I have read the attached protocol 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)", dated **17 October 2016**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice set forth in 21 CFR Parts 11, 50, 54, 56, and 312, and applicable regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc and (for Japanese sites only) of Daiichi Sankyo Co., Ltd.

_____
Signature

_____ _____
Name of Principal Investigator Date (DD Month YYYY)

For Japanese Sites Only:

I, as representative of Daiichi Sankyo Co., Ltd., agree to the provisions described in this protocol.

_____
Signature

_____ _____
Printed Name Date (DD Month YYYY)

Vice President,
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Department
Daiichi Sankyo Co., Ltd.

Protocol Synopsis

Title: 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)

Study Phase: 3

Indication: Adjuvant treatment for women with early-stage breast cancer at high risk of disease recurrence receiving standard of care adjuvant/neoadjuvant cancer therapy

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Primary Objective: (see Section 1.1)

To compare the treatment effect of denosumab with that of placebo on prolonging bone metastasis-free survival (BMFS) in subjects with early-stage breast cancer at high risk of disease recurrence

Secondary Objectives: (see Section 1.2)

To compare the treatment effect of denosumab with that of placebo on:

- Disease-free survival (DFS) in the full study population
- DFS in the postmenopausal subset
- Overall survival (OS)
- Distant recurrence-free survival (DRFS)

Safety Objectives: To assess the safety and tolerability of denosumab compared with placebo.

Exploratory Objectives: (see Section 1.3)

To evaluate the treatment effect of denosumab compared with placebo on:

- Time to first bone metastasis (excluding deaths)
- Time to bone metastasis as site of first recurrence
- Time to disease recurrence (TTR)
- Time to distant recurrence
- Time to first on-study fracture (vertebral or non-vertebral fracture)
- Time to first on-study skeletal-related event (SRE; following the development of bone metastasis)
- Time to first on-study SRE or hypercalcemia (following the development of bone metastasis)
- Time to first on-study symptomatic bone metastasis
- Brief Pain Inventory - Short Form (BPI-SF) ‘worst’ pain score
- BPI-SF pain severity and pain interference scales
- EQ-5D health index scores
- Analgesic use
- Breast density
- Pathological variables in tumor tissue from neoadjuvant subjects after surgery
- Pharmacokinetics
    - Serum trough levels of denosumab
- Pharmacodynamic response
    - Levels and dynamics of bone turnover markers and potential other pharmacodynamic markers

To investigate other potential biomarker development (eg, biochemical levels and abundance of drug targets) by biochemical analysis of blood and/or tumor tissue, and correlate with treatment outcomes

To investigate the association of tumor genetic variations in cancer genes, drug/pathway target genes, and/or other biomarker genes with treatment outcomes.

To investigate the genetic variation in cancer genes, drug/pathway target genes, and/or other biomarker genes, and correlate with treatment outcomes (optional; requires separate informed consent)

Hypotheses: (see Section 2.6)

Primary Hypothesis: Denosumab in combination with standard of care adjuvant/neoadjuvant cancer treatment will improve BMFS compared with standard of care treatment alone, as measured by the BMFS HR. It is anticipated that the true HR of denosumab compared with placebo is 0.8.

Secondary Hypothesis: Denosumab in combination with standard of care adjuvant/neoadjuvant cancer treatment will improve DFS compared with standard of care treatment alone in the full study population or in the postmenopausal subset, as measured by the DFS HR. It is anticipated that the true HR of denosumab compared with placebo is 0.83 in the full study population and 0.76 in the postmenopausal subset.

Study Design: (see Section 3.1)

This is an international, phase 3, randomized, double-blind, placebo-controlled study in women with early-stage (stage II or III) breast cancer at high risk of disease recurrence.

Approximately 4,500 subjects will be randomized in a 1:1 ratio to receive denosumab 120 mg or matching placebo subcutaneously (SC) every 4 weeks (Q4W) for approximately 6 months followed by denosumab 120 mg or matching placebo SC every 3 months (Q3M; ie**,** every 12 weeks) for 4½ years (approximately 54 months), for a total treatment duration of 5 years (approximately 60 months). During the first approximate 6 months of treatment, investigational product (denosumab or matching placebo) may be administered Q3W to subjects receiving or scheduled to receive Q3W adjuvant/neoadjuvant chemotherapy, to minimize patient clinic visits and enhance adherence to treatment. There must be at least a 3-week interval between administrations of investigational product. All subjects will be required to receive vitamin D and calcium supplementation at standard doses (at least 500 mg calcium and at least 400 IU of vitamin D; see Section 6.7), unless documented hypercalcemia develops on study. Subjects who develop bone metastasis will permanently discontinue investigational treatment, complete the End of Treatment Phase (EOTP) visit, and enter **long-term** follow-up **(LTFU)** upon documented evidence (per central imaging analysis or biopsy). **For an individual subject, the maximum duration of LTFU after completing the EOTP visit is 5 years (total study duration for an individual subject is up to 10 years from the date of randomization).**

Randomization will be stratified based on:

1. Breast cancer therapy / Lymph node (LN) status: neo-adjuvant therapy / any LN status versus [vs] adjuvant therapy / LN negative (based on axillary LN dissection, or based on sentinel node [SN] status) vs adjuvant therapy / LN positive
2. Hormone receptor (estrogen receptor [ER]/ progesterone receptor [PR]) status: ER and/or PR positive vs ER and PR negative
3. Human epidermal growth factor receptor 2 (HER-2) status: HER-2 positive vs HER-2 negative
4. Age: < 50 vs ≥ 50
5. Geographic Region: Japan vs Other

A data monitoring committee (DMC) external to Amgen and external to Daiichi Sankyo Co., Ltd. will review safety data at regular intervals, as outlined in the DMC charter (approximately twice yearly; the start date will depend on subject accrual rates), and will conduct **1** interim

analysis of efficacy after approximately 367 subjects have developed bone metastasis or died, and approximately 555 subjects have developed any disease recurrence or died, whichever comes last. Th**is** interim analys**is** may be conducted early, as soon as approximately 6 months after the sufficient event number has been reached for either BMFS or DFS in the full study population, even if the event number for the other endpoint has not been reached.

The primary analysis will be conducted after **all enrolled subjects have had the opportunity to complete 5 years of treatment from study day 1.**

Primary Endpoint: (see Section 10.2)

- BMFS (determined by the time from randomization to the first observation of bone metastasis or death from any cause)

Secondary Endpoints: (see Section 10.2)

- DFS in the full study population (determined by the time from randomization to the first observation of disease recurrence or death from any cause)
- DFS in the postmenopausal subset
- OS (determined by the time from randomization to death from any cause)
- DRFS (determined by the time from randomization to the first observation of distant metastasis or death from any cause)

Safety Endpoints: (see Section 10.2)

- Subject incidence of treatment-emergent adverse events
- Changes in laboratory values
- Subject incidence of anti-denosumab neutralizing antibody formation

Exploratory Endpoints: (see Section 10.2)

- Time to first bone metastasis (excluding deaths) (determined by the time from randomization to the first observation of bone metastasis as site of first or subsequent disease recurrence)
- Time to bone metastasis as site of first recurrence (determined by the time from randomization to the first observation of bone metastasis as site of first disease recurrence; excluding death)
- TTR (determined by the time from randomization to the first observation of disease recurrence; excluding death)
- Time to distant recurrence (determined by the time from randomization to the first observation of distant metastasis; excluding death)
- Time to first on-study fracture (determined by the time from randomization to the first observation of vertebral or non-vertebral fracture prior to the development of bone metastasis)
- Time to first on-study SRE (following the development of bone metastasis)
- Time to first on-study SRE or hypercalcemia (following the development of bone metastasis)
- Time to first on-study symptomatic bone metastasis
- BPI-SF ‘worst’ pain score
- BPI-SF pain severity and pain interference scales
- EQ-5D health index scores
- Analgesic use
- Breast density
- Pathological variables in tumor tissue from neoadjuvant subjects after surgery

- Pharmacokinetics
  - Serum trough levels of denosumab
- Pharmacodynamic response
  - Levels and dynamics of bone turnover markers and potential other pharmacodynamic markers
- Biochemical levels and abundance of drug targets in blood and/or tumor tissue, and correlate with treatment outcomes
- Association of tumor genetic variations in cancer genes, drug/pathway target genes, and/or other biomarker genes with treatment outcomes
- Analysis of genetic variations in cancer genes, drug/pathway target genes, and/or other biomarker genes, and correlate with treatment outcomes (optional; requires separate informed consent)

Sample Size: Approximately 4,500 subjects (2,250 subjects per arm) (see Section 3.3 and 10.3)

Summary of Subject Eligibility Criteria: (see Section 4.1 and 4.2)

Inclusion Criteria

- Histologically confirmed, AJCC stage II or III breast cancer

  See Appendix D *for breast cancer grading and staging information.*
- High risk of breast cancer recurrence, defined as documented evidence of one or more of the following criteria:
  - Biopsy evidence of breast cancer in regional LN (node positive disease)

    Nodal micrometastases only are not considered node positive
  - Tumor size > 5 cm (T3) or locally advanced disease (T4)

  See Appendix D *for breast cancer grading and staging information.*
- Documented pathological evaluation of the breast cancer for hormone receptor (ER and PR) status and HER-2 status
- Subjects must be receiving or be scheduled to receive standard of care systemic adjuvant or neoadjuvant chemotherapy and/or endocrine therapy and/or HER-2 targeted therapy
- For subjects receiving adjuvant therapy only:
  - Subjects must have undergone complete resection of the primary tumor with clean surgical margins, or

    Subjects must have undergone resection of the primary tumor and be scheduled for further treatment of the primary tumor with curative intent. Definitive treatment must be planned to be completed within approximately 9 months of randomization
  - Time between definitive surgery and randomization must be ≤ 12 weeks

    Definitive surgery may include secondary interventions (eg, to clear inadequate surgical margins)
  - Subjects with node positive disease must have undergone treatment of axillary LN with curative intent, or

    Subjects must be scheduled for further treatment of regional lymph nodes with curative intent. Definitive treatment must be planned to be completed within approximately 9 months of randomization
  - Subjects must not have received prior neoadjuvant treatment

    Endocrine treatment for less than 30 days prior to surgery is not considered prior neoadjuvant treatment

- For subjects receiving neoadjuvant therapy only:
    - Time between start of neoadjuvant treatment and randomization must be ≤ 8 weeks
    - Subjects must be scheduled to undergo definitive treatment (including surgery and/or radiotherapy) with curative intent within approximately 9 months of starting neoadjuvant treatment
- Female subjects with age ≥ 18 years
- Subjects with reproductive potential must have a negative pregnancy test within 14 days before randomization
- Serum calcium or albumin-adjusted serum calcium ≥ 2.0 mmol/L (8.0 mg/dL) and ≤ 2.9 mmol/L (11.5 mg/dL)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Written informed consent before any study-specific procedure is performed

Exclusion Criteria

- Prior or current evidence of any metastatic involvement of any distant site
- History of breast cancer (other than ductal carcinoma in situ [DCIS] or lobular carcinoma in situ [LCIS]) prior to the current diagnosis
- Osteoporosis requiring treatment at the time of randomization or treatment considered likely to become necessary within the subsequent six months
- Any prior or synchronous malignancy (other than breast cancer), except:
    - Malignancy treated with curative intent and with no evidence of disease for ≥ 5 years prior to enrollment and considered to be at low risk for recurrence by the treating physician
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Active infection with Hepatitis B virus or Hepatitis C virus
- Known infection with human immunodeficiency virus (HIV)
- Prior history or current evidence of osteomyelitis/osteonecrosis of the jaw
- Active dental or jaw condition which requires oral surgery
- Planned invasive dental procedure for the course of the study
- Non-healed dental or oral surgery
- Use of oral bisphosphonates within the past 1 year
- Prior or current IV bisphosphonate administration
- Prior administration of denosumab
- Subject currently is enrolled in or has not yet completed at least 30 days since ending other investigational device or investigational drug study(s), or subject is receiving other investigational agent(s)
- Subject is pregnant or breast feeding, or planning to become pregnant within 5 months after the end of treatment.
- Subject is of child bearing potential and is not willing to use, in combination with her partner, 2 highly effective methods of contraception or abstinence during treatment and for 5 months after the end of treatment

- Subject has known sensitivity to any of the products to be administered during the study (eg, mammalian derived products, calcium, or vitamin D)
- Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures.
- Any major medical or psychiatric disorder that may prevent the subject from completing the study or interfere with the interpretation of the study results

Investigational Product Dosage and Administration: (see Section 6.1 and 11.1)

Investigational product (denosumab 120 mg or matching placebo) will be administered SC Q4W (± 7 days) for approximately 6 months followed by denosumab 120 mg or matching placebo SC Q3M (ie**,** every 12 weeks ± 14 days) for 4½ years (approximately 54 months), for a total treatment duration of 5 years (approximately 60 months).

During the first approximate 6 months of treatment, investigational product may be administered Q3W to subjects receiving or scheduled to receive Q3W adjuvant/neoadjuvant chemotherapy, to minimize patient clinic visits and enhance adherence to treatment. There must be at least a 3-week interval between administrations of investigational product.

All subjects will be required to receive vitamin D and calcium supplementation at standard doses (at least 500 mg calcium and at least 400 IU of vitamin D; see Section 6.7), unless documented hypercalcemia develops on study.

Administration of investigational products (denosumab or placebo) will be withheld for any subject who experiences a grade 3 or 4 adverse event per Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 reported by the investigator as related to investigational product, **atypical femoral fracture (AFF)** or osteonecrosis of the jaw (ONJ)**,** as determined by the investigator or by an independent expert panel. Re-exposure to investigational products may occur only when the event resolves to grade 1 or less or the subject's baseline and if the investigator and sponsor agree subject safety will not be compromised. Administration of investigational product (denosumab or placebo) will also be withheld 30 days prior to any elective invasive oral/dental procedure. Investigational product administration will be withheld until documented evidence of complete mucosal healing following any invasive oral/ dental procedure.

Subjects who develop bone metastasis will permanently discontinue treatment, complete the EOTP visit, and enter follow-up upon documented evidence (per central imaging analysis or biopsy).

Control Group: Matching placebo (see Section 3, 5, 6, and 10).

Key Study Procedures: (see Section 7 and [Appendix A])

Informed consent must be obtained before any study specific procedures are performed.

Screening: Subjects enter the screening period once they have signed the informed consent form. Upon consent and once a call is placed to the interactive voice response system (IVRS) a unique subject identification number will be assigned. Subjects who do not meet eligibility criteria within the 28 day screening period will not be eligible for enrollment (ie randomization via IVRS), but may be rescreened once at the discretion of the investigator. See Section 5.1 for general information, and Section 7.1.1 for information regarding screening procedures.

Randomization: Upon completing all screening assessments and meeting all eligibility criteria, subjects will be randomized in a stratified manner to 1 of 2 treatment groups (denosumab or placebo) within 8 days before the day of first dose of investigational product (study day 1).

Treatment and Follow-up: Subjects will receive investigational product for up to 5 years from study day 1 (treatment period), and will **then enter LTFU for approximately 5 years (60 months) following the EOTP visit. The expected total study duration for an individual subject is up to 10 years from the randomization date.**

Subjects who withdraw early from investigational product administration will continue on-study procedures without investigational product administration according to the schedule of assessments for up to 5 years from study day 1 before entering follow-up.

Subjects who develop bone metastasis will permanently discontinue treatment, complete the EOTP visit, and enter follow-up upon documented evidence (per central imaging analysis or biopsy).

Assessments:

The following assessments will be performed at various visits (see Appendix A): medical and medication history; ECOG performance status; physical examination including vital signs (temperature, pulse, blood pressure, respiratory rate), height (at screening only) and weight; oral examination; clinical fractures and SREs; breast cancer therapy; concomitant medications; PRO questionnaires (including BPI-SF and EQ-5D); disease assessments including full body radioisotope bone scan, mammography (except after total mastectomy, in which case only the remaining breast [if applicable] must be imaged), and CT or MRI of the chest, abdomen and all other known or suspected sites of disease (positive bone scans must be confirmed using plain X-ray, CT, MRI or biopsy); pregnancy test; hematology; serum chemistry; denosumab PK (selected sites / subjects only); anti-denosumab antibodies; blood biomarkers and bone-specific alkaline phosphatase (BSAP); urine samples; tumor tissue collection (obtained as part of routine clinical care). Adverse events and concomitant medications will be recorded throughout the study.

Statistical Considerations: (see Section 10)

Key study objectives: The primary objective of this study is to compare the treatment effect of denosumab with that of placebo on prolonging BMFS in subjects with early-stage breast cancer at high risk of recurrence. The key secondary objective is to compare the treatment effect of denosumab with that of placebo on prolonging DFS in the full study population **and** in the postmenopausal subset.

Key efficacy analyses: **One** interim analys**i**s of efficacy will be conducted; after approximately 367 subjects have developed bone metastasis or died, and approximately 555 subjects in the full study population have developed any disease recurrence or died, whichever comes last. Th**is** interim analys**i**s may be conducted early, as soon as approximately 6 months after the sufficient event number has been reached for either BMFS or DFS in the full study population, even if the event number for the other endpoint has not been reached.

The primary analysis will be **conducted after all enrolled subjects have had the opportunity to complete 5 years of treatment from study day 1.**

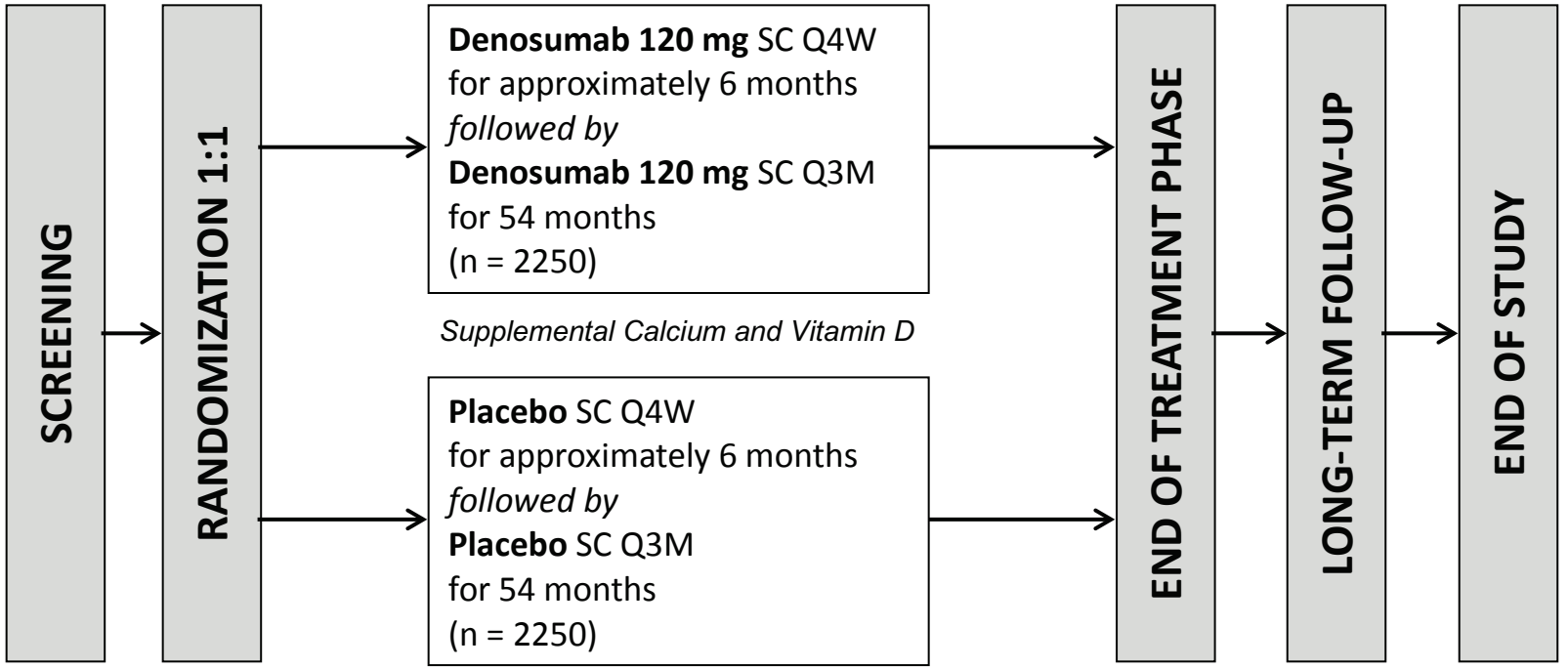
The primary efficacy endpoint, BMFS, will be analyzed using a log rank test stratified by the randomization stratification factors. The hazard ratio of denosumab compared with placebo and its corresponding 95% confidence interval will be estimated by use of a Cox proportional hazards model with treatment group as the independent variable stratified by the randomization stratification factors. If denosumab is determined to be superior to placebo with respect to the primary efficacy endpoint, the secondary efficacy endpoints, including

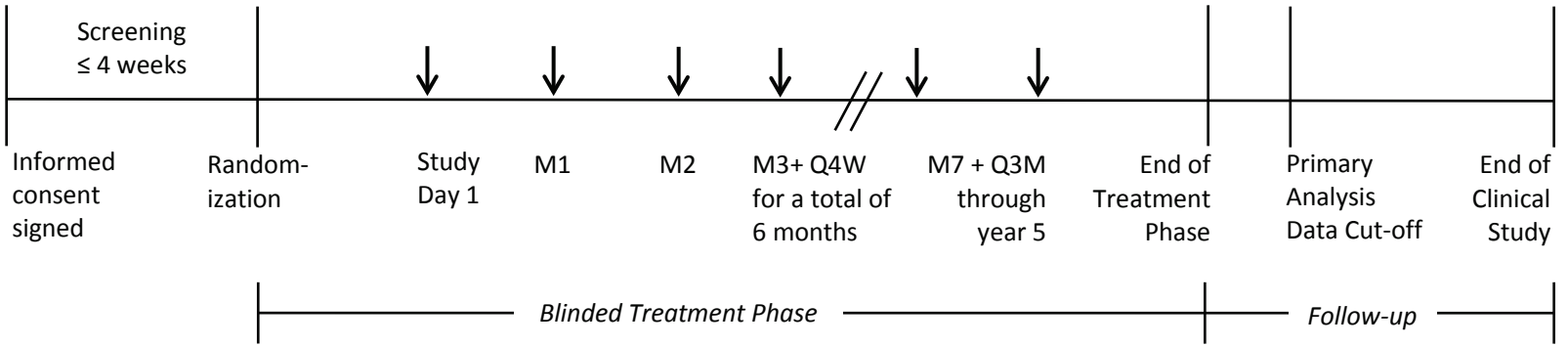
- Step 1: DFS in the full study population and DFS in the postmenopausal subset
- Step 2: OS
- Step 3: DRFS

will be tested in a stepwise fashion over 3 steps; ie**,** the treatment effect with respect to the secondary endpoints at the subsequent step will be tested only when denosumab is determined to be superior to placebo with respect to all the secondary endpoints at previous steps. At Step 1, DFS in the full study population and DFS in the postmenopausal subset will be tested simultaneously using a Hochberg procedure to adjust for multiplicity. The secondary endpoints at the subsequent step will be analyzed using a similar stratified log rank test and Cox proportional hazards model.

Safety will be evaluated by incidence and severity of adverse events, and toxicity grade shift in laboratory values. The number and percentage of patients who develop neutralizing anti-denosumab antibodies will be tabulated by study visit.

Study Schema





Study Glossary

Abbreviation or Term	Definition / Explanation
AJCC	American Joint Committee on Cancer
AFF	Atypical femoral fracture
AQA	Analgesic quantification algorithm
BCE	Bone collagen equivalents
BMFS	Bone metastasis-free survival
BPI-SF	Brief Pain Inventory – Short Form
BSAP	Bone-specific alkaline phosphatase
Cr	Creatinine
CRF	Case report form
CT	Computed tomography
(NCI) CTCAE	(National Cancer Institute) Common Terminology Criteria for Adverse Events
αCTX	C-telopeptide of type 1 collagen
DCARE	Denosumab as Adjuvant Treatment for Women with Early-Stage Breast Cancer at High Risk of Recurrence
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DRFS	Distant recurrence-free survival
E_{max}	Maximal effect
eCRF	Electronic case report form
EDC	Electronic Data Capture
EQ-5D	EuroQol 5-Dimension; a health utility questionnaire
ER	Estrogen receptor
eSAE	Electronic Serious Adverse Event
(b)FGF	Basic fibroblast growth factor
ECOG	Eastern Cooperative Oncology Group
EOTP	End of Treatment Phase
EU	**European Union**
FAS	Full analysis set
GCP	Good Clinical Practice
HER-2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hazard ratio

Abbreviation or Term	Definition / Explanation
IC_{90}	90% inhibitory concentration
ICH GCP	International Conference on Harmonisation and Good Clinical Practice
IDFS	Invasive DFS
IEC	Independent ethics committee
IgG2	Immunoglobulin G2
IRB	Institutional review board
IV	Intravenous
IVRS	Interactive voice response system (or, for Japan only, interactive web response system)
K_d	Dissociation constant
kg	Kilogram
K-M	Kaplan-Meier
LCIS	Lobular carcinoma in situ
LN	Lymph node
LSP	Lactation Surveillance Program
LTFU	**Long-term follow-up**
µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHLW	Ministry of Health, Labor and Welfare (Japan)
mL	Milliliter
mm	Millimeter
mM	Millimolar
min	Minutes
MPA	Medroxy-progesterone acetate
MRI	Magnetic resonance imaging
nM	Nanomolar
NTx	N-telopeptide of type I collagen
ONJ	Osteonecrosis of the jaw
OPG	Osteoprotegerin
OS	Overall survival
P1NP	Procollagen type 1 N-propeptide
PIN	Personal identification number
PK	Pharmacokinetic(s)

Abbreviation or Term	Definition / Explanation
PR	Progesterone receptor
PRO	Patient Reported Outcome
PSP	Pregnancy Surveillance Program
Q3M	Every 3 months (ie, every 12 weeks ± 14 days)
Q3W	Every 3 weeks
Q4W	Every 4 weeks (± 7 days)
Q12W	Every 12 weeks
SAE	Serious adverse event
SAER	Serious adverse event report
SAP	Statistical analysis plan
SC	Subcutaneous
SN	Sentinel (lymph) node
SRE(s)	Skeletal-related event(s); defined as any fracture (vertebral or non-vertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression following the development of bone metastasis
SUSAR	suspected unexpected serious adverse reactions
TNF	Tumor necrosis factor
TRAP5b	Tartate-resistant Acid Phosphatase 5b
TTR	Time to disease recurrence
ULN	Upper limit of normal
uNTx	Urinary N-telopeptide of type I collagen
VEGF	Vascular endothelial growth factor

Definitions

Term	Definition/Explanation
Treatment Phase	Period when the subject is receiving study treatment (up to 5 years from study day 1). Subjects who withdraw early from investigational product administration will continue on-study procedures without investigational product administration according to the schedule of assessments for up to 5 years from study day 1 before entering follow-up.
Primary Analysis Data Cut-off Date (primary completion)	Amgen will set a primary analysis data cut-off date in anticipation of **all enrolled subjects having had the opportunity to complete 5 years of treatment from study day 1**. The primary analysis will be based on the data from randomization through the primary analysis data cut-off date.
End of Study (for the clinical study)	The date that the last subject is assessed in the follow-up phase.
Screening Period (for an individual participant)	Subjects enter the screening period once they have signed the informed consent form. See Section 5.1 for general information, and Section 7.1.1 for information regarding Screening Procedures.
Randomization	Subjects will be randomly assigned by the IVRS to either blinded denosumab or matching placebo
Enrollment	A subject is considered enrolled upon randomization via the interactive voice response system (IVRS).
Study Day 1	Day of first dose of investigational product (denosumab or matching placebo)
Study Treatment	Investigational product (denosumab or matching placebo)
End of Investigational Product	The date of the last dose of investigational product (denosumab or placebo) treatment.
Hypercalcemia	Albumin-adjusted serum calcium > 2.9 mmol/L (11.5 mg/dL) or ionized calcium > 1.5 mmol/L
End of Treatment Phase (EOTP) (for an individual participant)	An individual subject may receive investigational product for up to 5 years (ie, 60 months) from the day of first dose of investigational product (study day 1), or until documented evidence of bone metastasis (per central imaging analysis or biopsy), whichever is earlier. See Section 3.4.1.

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1. OBJECTIVES

1.1 Primary

To compare the treatment effect of denosumab with that of placebo on prolonging bone metastasis-free survival (BMFS) in subjects with early-stage breast cancer at high risk of recurrence

1.2 Secondary

To compare the treatment effect of denosumab with that of placebo on:

- Disease-free survival (DFS; determined by the time from randomization to the first observation of disease recurrence or death from any cause) in the full study population
- DFS in the postmenopausal subset
- Overall survival (OS)
- Distant recurrence-free survival (DRFS)

Safety Objectives

- To assess the safety and tolerability of denosumab compared with placebo

1.3 Exploratory

To evaluate the treatment effect of denosumab compared with placebo on:

- Time to first bone metastasis (excluding deaths)
- Time to bone metastasis as site of first recurrence
- Time to disease recurrence (TTR)
- Time to distant recurrence
- Time to first on-study fracture (vertebral or non-vertebral fracture)
- Time to first on-study skeletal-related event (SRE; following the development of bone metastasis)
- Time to first on-study SRE or hypercalcemia (following the development of bone metastasis)
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- Pathological variables in tumor tissue from neoadjuvant subjects after surgery
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  - Serum trough levels of denosumab
- Pharmacodynamic response
  - Levels and dynamics of bone turnover markers and potential other pharmacodynamic markers

To investigate other potential biomarker development (eg, biochemical levels and abundance of drug targets) by biochemical analysis of blood and/or tumor tissue, and correlate with treatment outcomes.

To investigate the association of tumor genetic variations in cancer genes, drug/pathway target genes, and/or other biomarker genes with treatment outcomes

To investigate the genetic variation in cancer genes, drug/pathway target genes, and/or other biomarker genes, correlate with treatment outcomes (optional; requires separate informed consent)

2. BACKGROUND AND RATIONALE

2.1 Breast Cancer

Breast cancer affects more than one million women annually worldwide and is the most common cause of cancer death in women aged 20 to 60 (Jemal et al., 2008; Garcia et al., 2007). In 2008, in the United States, an estimated 182,450 women were diagnosed with breast cancer, with approximately 40,493 deaths (Jemal et al., 2008). Although most patients present with disease that appears localized to the breast, a significant proportion of women will eventually develop metastases. Indeed, micro-metastases can be detected in the bone marrow of patients with primary breast cancer after surgery and before initiation of adjuvant treatment (Muller et al., 2005). Adjuvant systemic therapy is considered standard of care for breast cancer patients at high risk for recurrence based on prognostic factors: primary tumor size, metastasis to regional lymph nodes, histologic or nuclear grade, cell surface and steroid hormone receptor expression as well as gene signature (Carlson et al., 2008).

Bone is the most frequent site of distant relapse, accounting for approximately 40% of all first distant recurrences; up to 80% of stage IV breast cancer patients eventually develop disease in the bone (Coleman, 2007). Skeletal metastasis is associated with significant long-term morbidity, including pathologic fractures in around 50% of patients, pain, and spinal cord compression. These events have a significant impact on the quality of life of patients (Lipton, 2003). The pathophysiology of establishing bony metastases of breast cancer is thought to depend on a vicious cycle, where growth factors and cytokines, released from cancer cells and bone, activate osteoclasts to induce bone resorption (Yoneda et al., 2003). Activated osteoclasts and resorbing bone in turn release growth factors that create an environment conducive for the establishment of metastatic deposits. Cancer cells homing to the bone surface are stimulated to grow and proliferate; their offspring may re-enter the circulation and metastasize to distant sites,

repopulate fully treated primary sites, or generate apparent second primary lesions (Bidard et al., 2008). Inhibition of osteoclast activity is therefore a rational strategy to alter the bone microenvironment and prevent the development of both, bony and visceral metastases.

2.2 Bone-targeted Treatment in Adjuvant Breast Cancer

2.2.1 Bisphosphonates in Adjuvant Breast Cancer

Long-term follow-up data from several trials with bisphosphonates have been reported: Powles et al demonstrated a significant reduction in the occurrence of bone metastases at 2 years and at 5 years with oral clodronate (1,600 mg/day for 2 years), as compared with placebo; with hazard ratios (HR)=0.546 (0.312, 0.954; p=0.031) and HR=0.692 (0.484, 0.990; p=0.043), respectively. These differences were most pronounced in higher risk patients (patients with stage II/III disease compared to stage I disease). Survival data showed a trend in favor of the clodronate arm (HR [all patients]=0.768, p=0.048; HR [stage II/III disease]=0.743, p=0.041), although results did not reach statistical significance due to multiple analyses (Powles et al., 2006). In a second study, Diel et al reported a significantly lower incidence of osseous metastases (12 [8%] versus 25 [17%] patients, p<0.003), and of visceral metastases (13 [8%] versus 27 [19%] patients, p<0.003) in the clodronate group versus the control group (Diel et al., 1998). In contrast, Saarto et al reported no significant difference in BMFS between the clodronate and placebo groups, and a significantly lower DFS due to increased development of non-skeletal metastases in the clodronate-treated group (Saarto et al., 2008; Saarto et al., 2004). Definitive studies of clodronate in early-stage breast cancer are ongoing. ABCSG-12 was the first large, prospective clinical trial to demonstrate an anticancer benefit with zoledronic acid in the early breast cancer setting (Gnant et al., 2009). In ABCSG -12, 1803 premenopausal women with estrogen-receptor-positive breast cancer treated with goserelin to induce menopause and either tamoxifen or anastrozole were randomly assigned to 6-monthly zoledronic acid 4 mg for 3 years or no additional treatment. The primary endpoint was DFS; recurrence-free survival and OS were secondary end points. The final analysis after 94.4 months median follow-up (range 0 to 114 months), including 251 (13.9%) DFS events and 86 (4.8%) OS events, showed that the addition of zoledronic acid to endocrine therapy significantly reduced the risk of DFS events by 23% (HR=0.77 [0.60, 0.99]; p=0.042) (Gnant et al., 2015). There were fewer disease recurrences overall in the zoledronic acid versus no-zoledronic acid group (111 versus 140), with the greatest reductions in locoregional recurrences (25 versus 40), distant recurrences

(58 versus 67), and bone metastases (27 versus 35), indicating that the anticancer effects of treatment were not confined to bone. Furthermore, a prespecified exploratory subgroup analysis by age at study entry suggests that zoledronic acid reduced the relative risk of disease progression in patients >40 years but not ≤40 years of age. For OS, there was a non-significant trend in favor of zoledronic acid treatment (HR=0.66 [0.43, 1.02]; p=0.064).

Similar to ABCSG-12, the AZURE trial was designed with DFS as the primary endpoint (Coleman et al., 2011). In this phase 3 trial (n=3360), the use of adjuvant zoledronic acid was evaluated in stage II-III breast cancer patients randomized to adjuvant systemic therapy with or without zoledronic acid, 4 mg administered every 3 to 4 weeks for 6 doses, and then every 3 months for 8 doses followed by every 6 months for 5 doses, for a total of 5 years of treatment. Results from the intention-to-treat final analysis of this fully recruited study was reported after a median follow-up of 84 months (Coleman et al., 2014). The number of DFS events did not differ between the groups, with 493 in the control group and 473 in the zoledronic acid group (adjusted HR=0.94 [0.82-1.06]; p=0.30). Invasive DFS (IDFS), OS, and distant recurrences were much the same in both groups. However, zoledronic acid improved IDFS in patients who were over 5 years since menopause at trial entry (n=1041, HR=0.77 [0.63-0.96]) but not in all other menopausal groups (premenopause, perimenopause, and unknown status) (n=2318, HR=1.03 [0.89-1.20]). Zoledronic acid also reduced the development of bone metastases, both as a first event (HR=0.78 [0.63-0.96]; p=0.020) and at any time during follow-up (HR=0.81 [0.68-0.97]; p=0.022). Initially, these results seemed inconsistent with data from the ABCSG-12 study in premenopausal women. However, due to ovarian function suppression, all subjects were amenorrheic and the estrogen levels of subjects in ABCSG-12 were therefore likely similar to the postmenopausal subset in the AZURE study.

2.2.2 Denosumab in Adjuvant/Neoadjuvant Breast Cancer

Refer to Section 2.5 for the rationale for developing denosumab in adjuvant/neoadjuvant breast cancer.

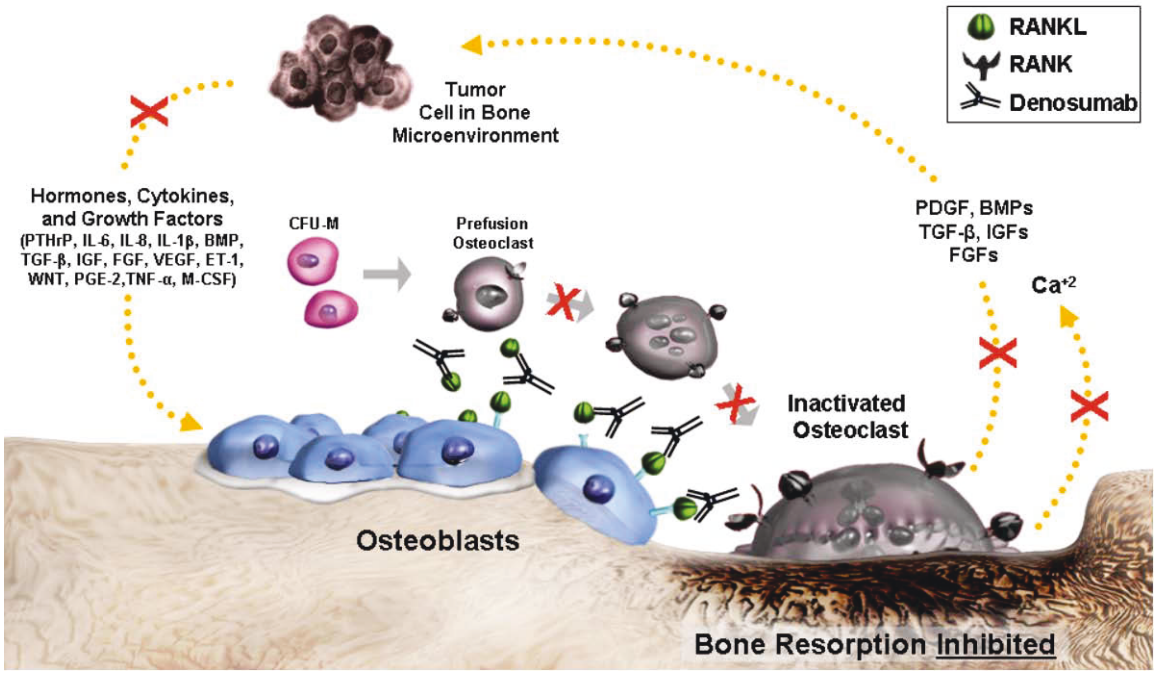
2.3 Denosumab Background

Perturbations in the balance between bone formation and resorption can lead to generalized osteoporosis (resulting from estrogen deficiency and aging) or local bone lysis (resulting from rheumatoid arthritis and bone metastases). The RANK-RANK ligand system has been identified as an essential mediator of osteoclast formation, function, and survival (Teitelbaum et al, 2003). RANK ligand binds RANK on osteoclasts or osteoclast precursors to stimulate or promote differentiation into osteoclasts and activate mature osteoclasts to resorb bone. Therefore, RANK ligand is a therapeutic target for diseases associated with increased bone resorption.

Denosumab is a fully human monoclonal IgG2 antibody to RANK ligand that binds with high affinity and specificity to RANK ligand (Kd 3 x 10^{-12} M). This binding prevents the activation of RANK and inhibits the formation, activation, and survival of osteoclasts, the result of which is a reduction in the number and function of osteoclasts and, consequently, a decrease in bone resorption and an increase in cortical and trabecular bone mass, volume, and strength (Kostenuik, 2005) (Figure 1). Denosumab is highly specific because it binds only to RANK ligand and does not bind to other members of the tumor necrosis factor (TNF) family, including TNFα, TNFβ, TNF-related apoptosis-inducing ligand, or CD40 ligand (Elliott et al, 2006).

Refer to the latest version of the investigator brochure for additional and updated information on denosumab background, clinical experience, and safety information.

Figure 1. Mechanism of Action of Denosumab (adapted from Clezardin and Teti, 2007)



2.4 Denosumab Dose and Schedule Selection

The selection of dose and schedule for denosumab is based on the seriousness and expected clinical outcomes of the disease indication, as well as pharmacokinetic (PK), pharmacodynamic, safety and tolerability data. In patients with early-stage (stage II or III) breast cancer at a high risk of recurrence, the standard duration of adjuvant chemotherapy is 6 months, with continued endocrine treatment (as applicable) for at least 5 years, which has been shown to significantly lower the risk of recurrence and improve overall survival compared with either shorter treatment durations or no treatment (EBCTCG, 2005). Thus, the dosing algorithm for prevention of bone metastasis in this patient population should ensure optimal efficacy during the first 6 months, with a total treatment duration of at least 5 years.

Based on safety, PK and pharmacodynamic data from phase 1 and 2 studies, a dosing regimen of denosumab 120 mg SC Q4W for approximately 6 months followed by 120 mg SC Q12W (Q3M) for 4 ½ years (approximately 54 months) is proposed. Specifically, Study 20040113 tested five different dosing schedules of SC denosumab versus IV bisphosphonates in 255 patients with breast cancer and bone metastases: 30 mg, 120 mg or 180 mg SC given Q4W, and 60 mg or 180 mg given Q12W (Lipton et al., 2007; Lipton et al., 2008). The regimen of 120 mg Q4W was associated with the greatest median reduction of the bone turnover marker uNTX at week 13, the primary endpoint of the study. Unlike lower doses, the 120 mg Q4W schedule avoided

low drug exposure, which could potentially translate into insufficient efficacy in some patients. Denosumab was found to be safe and well tolerated in all study arms.

A population PK/pharmacodynamic (inhibition of uNTX/Cr) model was developed using 25-week interim data from Study 20040113. In this two-compartment model with first-order absorption following SC administration and parallel linear and saturable (Michaelis-Menten) eliminations, pharmacodynamics were described by a sigmoidal E_{max} inhibition of synthesis model, where changes in the uNTx/Cr ratio were modeled as a function of denosumab serum concentrations. This model was used to perform simulations to predict pharmacokinetics and uNTX/Cr values in 2,000 patients using the proposed dose regimen. Dosing of 120 mg Q4W denosumab during the first approximate 6 months is predicted to result in maximal suppression of uNTX/Cr (≤ 30 nM BCE/mM) over the entire dose interval in 95% of treated subjects. Dosing of 120 mg Q12W for the remaining treatment period is predicted to maintain suppression of uNTX/Cr below approximately 50 nM BCE/mM in 95% of treated subjects. Cancer patients with bone metastases on bisphosphonate treatment with uNTx/Cr levels greater than 50 nM BCE/mM were found to have 2-fold or greater risk of skeletal complications and disease progression relative to those with levels < 50 nM BCE/mM (Coleman et al., 2005). Thus, the 120 mg Q12W dose regimen is considered appropriate after the first approximate 6 months, because it provides for less frequent dosing that is likely beneficial for patient convenience and treatment compliance, yet maintains effective suppression of bone resorption in a high proportion of subjects.

Therefore, denosumab 120 mg SC will be administered Q4W (ie, every 4 weeks ± 7 days) for the first approximate 6 months, followed by denosumab 120 mg SC every 3 months (Q3M; ie, every 12 weeks ± 14 days) for an additional 4 ½ years (approximately 54 months), for a total treatment duration of 5 years.

2.5 Rationale for Developing Denosumab in Adjuvant/Neoadjuvant Breast Cancer

Several lines of evidence support developing denosumab in this setting: denosumab is a potent inhibitor of osteoclast formation, function and survival. Osteoclasts have a role in the establishment and progression of bone metastasis via the vicious cycle. This is supported by experimental inhibition of RANKL in rodent models (using the soluble receptor osteoprotegerin [OPG]-Fc), which not only prevents tumor-induced osteolysis and decreases progression of established breast cancer skeletal tumors in mice (Canon, Roudier et al., 2008), but also significantly delayed de novo formation of breast

cancer skeletal metastases (Canon, Bryant et al., 2008). In addition, RANK is expressed in human breast tumors, and is functional on breast cancer cells (Roudier et al., 2006). Signaling through RANK/RANKL regulates the development of the mouse mammary gland during pregnancy. Transgenic mice overexpressing murine RANK exhibit increased mammary tumorigenesis relative to wild type mice in both induced (medroxyprogesterone acetate [MPA] + 1,7-dimethyl-benz(a) anthracene [DMBA]) and spontaneous (multiple pregnancies) models of mammary tumorigenesis. RANK expression is associated with an increased incidence of more extensive ductular hyperplasia and mammary intraepithelial neoplasia, an increased incidence of adenocarcinoma, as well as a shorter latency to tumor formation and increased numbers of tumors per gland and per mouse (Gonzalez-Suarez et al., 2006). Conversely, inhibition of the RANK/RANKL axis reduces hormone-induced mammary epithelial proliferation and reduces the incidence of mammary tumors (Branstetter et al., 2008). These observations support the hypothesis that inhibition of RANKL with denosumab may delay the development of clinical metastasis and disease recurrence in early-stage breast cancer.

Recently published clinical data indicate that the benefits of bisphosphonates in the adjuvant breast cancer setting are restricted to a postmenopausal subgroup of patients (Azim et al., 2013). If these positive effects are attributed to the antiresorptive effects of bisphosphonates, then a more potent antiresorptive like denosumab would be expected to achieve similar results. The underlying mechanism for a potential antitumor effect of adjuvant/neoadjuvant use of antiresorptive agents in breast cancer patients in a low estrogen state is unclear. One hypothesis is that estrogen depletion leads to accelerated bone resorption, which may hasten the vicious cycle theory of bone metastasis. As antiresorptive agents interrupt the vicious cycle, this effect might be more pronounced in the postmenopausal setting, where estrogen levels are lower. A preclinical study in animal models has shown that the postmenopausal state induced changes to the bone microenvironment such that the growth of disseminated breast cancer cells are triggered and that these changes could be prevented by anti-osteoclastic activity (Ottewell et al., 2014).

The purpose of this phase 3 study is to evaluate the ability of denosumab to prolong BMFS and DFS in breast cancer patients at high risk for disease recurrence, when combined with standard of care adjuvant/neoadjuvant cancer therapy.

2.6 Hypotheses

Primary Hypothesis: Denosumab in combination with standard of care adjuvant/ neoadjuvant cancer treatment will improve BMFS compared with standard of care treatment alone, as measured by the BMFS HR. It is anticipated that the true HR of denosumab compared with placebo is 0.8.

Secondary Hypothesis: Denosumab in combination with standard of care adjuvant/ neoadjuvant cancer treatment will improve DFS compared with standard of care treatment alone in the full study population or in the postmenopausal subset, as measured by the DFS HR. It is anticipated that the true HR of denosumab compared with placebo is 0.83 in the full study population **and 0.76** in the postmenopausal subset.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an international, phase 3, randomized, double-blind, placebo-controlled study in women with early-stage (stage II or III) breast cancer at high risk of disease recurrence. Approximately 4,500 subjects will be randomized in a 1:1 ratio to receive denosumab 120 mg or matching placebo SC Q4W (± 7 days) for approximately 6 months followed by denosumab 120 mg or matching placebo SC every Q3M (ie**,** every 12 weeks ± 14 days) for 4½ years (approximately 54 months), for a total treatment duration of 5 years (approximately 60 months). As there are approved bone-targeted therapies for the treatment of bone metastasis, subjects who develop bone metastasis will permanently discontinue investigational treatment, complete the End of Treatment Phase (EOTP) visit, and enter follow-up upon documented evidence (per central imaging analysis or biopsy).

During the first approximate 6 months of treatment, investigational product (denosumab or matching placebo) may be administered Q3W to subjects receiving or scheduled to receive Q3W adjuvant/neoadjuvant chemotherapy, to minimize patient clinic visits and enhance adherence to treatment. There must be at least a 3-week interval between administrations of investigational product. All subjects will be required to receive vitamin D and calcium supplementation at standard doses (at least 500 mg calcium and at least 400 IU of vitamin D; see Section 6.7), unless documented hypercalcemia develops on study.

A data monitoring committee (DMC) external to Amgen and external to Daiichi Sankyo Co., Ltd. will review safety data at regular intervals, as outlined in the DMC charter (approximately twice yearly; the start date will depend on subject accrual rates). This

external DMC will conduct **1** interim **analysis** of efficacy after approximately 367 subjects have developed bone metastasis or died, and approximately 555 subjects have developed any disease recurrence or died, whichever comes last**.** To ensure timely conduct of the interim **analysis**, the interim **analysis** may be conducted early, as soon as approximately 6 months after the sufficient event number has been reached for either BMFS or DFS in the full study population, even if the event number for the other endpoint has not been reached.

The primary analysis will be conducted after **all enrolled subjects have had the opportunity to complete 5 years of treatment from study day 1.**

The overall study design is described by a Schema at the end of the Protocol Synopsis section. Statistical considerations are outlined in Section 10.

3.2 Number of Centers

Approximately 500 investigative sites will participate in this study worldwide. If subject enrollment or enrollment projections are lower than expected, then additional sites may be recruited to ensure timely completion of the study. Sites that do not enroll at least one subject within 6 months of site initiation may be closed to future participation in the study.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. Approximately 2,250 subjects will be randomized to each treatment group, for a total planned sample size of approximately 4,500 subjects. Refer to Section 10.3 for details on the rationale for the number of subjects.

3.4 Estimated Study Duration

3.4.1 Study Duration for Individual Participants

An individual subject may receive investigational product treatment for up to 5 years (ie**,** 60 months) from the day of first dose of investigational product (study day 1), or until documented evidence of bone metastasis (per central imaging analysis or biopsy), whichever is earlier (treatment phase).

After completing the treatment phase of the study, subjects will be followed by clinic visit or telephone contact for up to **5** years (**60** months) from the **EOTP visit (total study duration for an individual subject is up to 10 years from the date of randomization)**. **Follow-up procedures are detailed in Section 7.1.4.**

Study treatment will cease if a subject experiences unacceptable toxicity, documented

disease recurrence in the bone (per central imaging analysis or biopsy), death, withdraws consent, or due to an administrative decision (by the investigator or Amgen, or [for Japanese sites only] Daiichi Sankyo Co., Ltd.).

Subjects who are discontinued from investigational product administration will continue all other on-study procedures without investigational product administration according to the schedule of assessments (Appendix A) for the remaining treatment period (60 months from study day 1) before entering follow-up.

3.4.2 Duration of the Clinical Study

The anticipated duration **from first subject enrolled to the primary completion of the study** is approximately **87** months (ie**,** 7 years and **3** months). This represents time to recruit approximately 4,500 subjects (approximately **27** months) and time for **all subjects to have the opportunity to complete 5 years of blinded treatment**.

The anticipated overall duration of the clinical study, including the recruitment period (approximately 2.5 years [**27** months]), the treatment period (approximately 5 years [60 months]**)**, and the follow-up period (approximately 5 years [60 months]), will be approximately 12.5 years or approximately 150 months.

3.4.3 End of Study (End of the Clinical Study)

Primary Completion

The primary analysis will be conducted after all enrolled subjects have had the opportunity to complete 5 years of treatment from study day 1. The primary analysis will be based on the data from randomization through the primary analysis data cut-off date and is considered the primary completion of the study.

End of Study (End of Clinical Study)

The End of Study (End of the Clinical Study) is defined as the date that the last subject is assessed in the follow-up phase. With **27** months of enrollment and the last subject anticipated to be on study for **up to** 10 years (ie, 120 months), the end of study is anticipated to be approximately 12.5 years (ie, approximately 150 months) from the first subject enrolled.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate's age and race, the date, and the outcome of the screening process (eg, enrolled into study,

reason for ineligibility, or refused to participate). Before any study-specific procedure, the appropriate written informed consent must be obtained (see Section 12.1).

4.1 Inclusion Criteria

Disease related

4.1.1 Histologically confirmed, AJCC stage II or III breast cancer [(1)]

See Appendix D for breast cancer grading and staging information.

4.1.2 High risk of breast cancer recurrence, defined as documented evidence of one or more of the following criteria: [(1)]

4.1.2.1 Biopsy evidence of breast cancer in regional lymph node(s) (LN) (node-positive disease)

Nodal micrometastases only are not considered node positive

4.1.2.2 Tumor size > 5 cm (T3) or locally advanced disease (T4)

See Appendix D for breast cancer grading and staging information.

4.1.3 Documented pathological evaluation of the breast cancer for hormone receptor (estrogen receptor [ER] and progesterone receptor [PR]) status and HER-2 status [(1)]

4.1.4 Subjects must be receiving or be scheduled to receive standard of care systemic adjuvant or neoadjuvant chemotherapy and/or endocrine therapy and/or HER-2 targeted therapy [(1)]

4.1.5 For subjects receiving adjuvant therapy only: [(1)]

4.1.5.1 Subjects must have undergone complete resection of the primary tumor with clean surgical margins, or

Subjects must have undergone resection of the primary tumor and be scheduled for further treatment of the primary tumor with curative intent. Definitive treatment must be planned to be completed within approximately 9 months of randomization

4.1.5.2 Time between definitive surgery and randomization must be ≤ 12 weeks

Definitive surgery may include secondary interventions (eg. to clear inadequate surgical margins)

4.1.5.3 Subjects with node positive disease must have undergone treatment of axillary LN with curative intent, or

Subjects must be scheduled for further treatment of regional lymph nodes with curative intent. Definitive treatment must be planned to be completed within approximately 9 months of randomization

4.1.5.4 Subjects must not have received prior neoadjuvant treatment

Endocrine treatment for less than 30 days prior to surgery is not considered prior neoadjuvant treatment

4.1.6 For subjects receiving neoadjuvant therapy only: [(1)]

4.1.6.1 Time between start of neoadjuvant treatment and randomization must be ≤ 8 weeks

4.1.6.2 Subjects must be scheduled to undergo definitive treatment (including surgery and/or radiotherapy) with curative intent within approximately 9 months of starting neoadjuvant treatment

Demographic

4.1.7 Female subjects with age ≥ 18 years [(1)]

Laboratory

4.1.8 Subjects with reproductive potential must have a negative pregnancy test within 14 days before randomization [(2)]

4.1.9 Serum calcium or albumin-adjusted serum calcium ≥ 2.0 mmol/L (8.0 mg/dL) and ≤ 2.9 mmol/L (11.5 mg/dL) [(3)]

General

4.1.10 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 [(3)]

4.1.11 Written informed consent before any study-specific procedure is performed [(4)]

Rationale for Inclusion Criteria

These criteria are included to

[(1)] ensure enrollment of representative subjects for the planned indication.

[(2)] prevent pregnancy during treatment

[(3)] minimize the risk for subject safety.

[(4)] ensure that the study will be conducted in compliance with Good Clinical Practice (GCP)

4.2 Exclusion Criteria

Disease related

4.2.1 Prior or current evidence of any metastatic involvement of any distant site[(1)]

4.2.2 History of breast cancer (other than ductal carcinoma in situ [DCIS] or lobular carcinoma in situ [LCIS]) prior to the current diagnosis[(1)]

Medical Conditions

4.2.3 Osteoporosis requiring treatment at the time of randomization or treatment considered likely to become necessary within the subsequent six months[(3)]

4.2.4 Any prior or synchronous malignancy (other than breast cancer), except:

- Malignancy treated with curative intent and with no evidence of disease for ≥ 5 years prior to enrollment and considered to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease[(3)]

4.2.5 Active infection with Hepatitis B virus or Hepatitis C virus[(2)]

4.2.6 Known infection with human immunodeficiency virus (HIV)[(2)]

Oral/ Dental Conditions

4.2.7 Prior history or current evidence of osteomyelitis/ osteonecrosis of the jaw[(2)]

4.2.8 Active dental or jaw condition which requires oral surgery[(2)]

4.2.9 Planned invasive dental procedure for the course of the study[(2)]

4.2.10 Non-healed dental or oral surgery[(2)]

Medications/ Treatments

4.2.11 Use of oral bisphosphonates within the past 1 year[3]

4.2.12 Prior or current IV bisphosphonate administration[3]

4.2.13 Prior administration of denosumab[3]

4.2.14 Subject currently is enrolled in or has not yet completed at least 30 days since ending other investigational device or investigational drug study(s), or subject is receiving other investigational agent(s)[2, 3]

General

4.2.15 Subject is pregnant or breast feeding, or planning to become pregnant within 5 months after the end of treatment[4]

4.2.16 Subject is of child bearing potential and is not willing to use, in combination with her partner, 2 highly effective methods of contraception or abstinence during treatment and for 5 months after the end of treatment[4]

4.2.17 Subject has known sensitivity to any of the products to be administered during the study (eg, mammalian derived products, calcium, or vitamin D)[2]

4.2.18 Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures[2, 5]

4.2.19 Any major medical or psychiatric disorder that in the opinion of the investigator might prevent the subject from completing the study or interfere with the interpretation of the study results[2, 5]

Rationale for Exclusion Criteria

These criteria are included to
[1] ensure enrollment of representative subjects for the planned indication
[2] minimize safety risks
[3] exclude potential confounding effects from the evaluation of the investigational drug.
[4] prevent pregnancy during treatment
[5] ensure that the study will be conducted in compliance with GCP

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written independent ethics committee (IEC)/institutional review board (IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 12.3). All subjects or legally acceptable representatives and the person who conducted the informed consent discussion must personally sign and date the informed consent form(s) before any study-specific procedures (including screening procedures) can be performed.

5.1 Screening

Subjects enter the screening period once they have signed the informed consent form. Upon consent and once a call is placed to the interactive voice response system (IVRS),

a unique subject identification number will be assigned. Procedures that have been performed prior to screening as part of routine care are not considered study-specific procedures. However, they may be used for screening purposes, if conducted within the timelines outlined in Section 7.2.

All subjects will be assigned a unique identification number before any study procedures are performed; it will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed at the time of rescreening, or randomization.

Refer to Section 7 and Appendix A for screening procedures and medical history details. Subjects may be re-screened once. If a subject fails to meet all entry criteria after 2 attempts, the subject may not be enrolled into the study.

Subjects who do not meet eligibility criteria within the 28 day screening period will not be eligible for enrollment. However, subjects may be rescreened once, at the discretion of the investigator. If a subject is being rescreened, the subject may need to reconsent to participate in the clinical study to ensure that the valid signed informed consent has been signed within 28 days prior to enrollment. Subjects who will be rescreened must be registered as screen failures via the IVRS, and registered as a rescreen. Subjects who will not be rescreened or are determined ineligible after rescreen, must be documented as screen failures and the reason for screen failure must be provided, by entering the screen failure reason in the IVRS.

The subject enrollment date is defined as the date that the subject meets all eligibility criteria and is randomized by the IVRS.

5.2 Treatment Assignment

A subject who gives written informed consent and who satisfies all inclusion and exclusion criteria may be randomized into the study. Questions about subject eligibility must be discussed and documented with Amgen or designee before randomization.

Upon confirmation of eligibility, the site will telephone IVRS in order to randomize the subject centrally to receive SC injections of denosumab or matching placebo. The IVRS will provide the caller with the box number for the investigational product and a subject randomization number that will be recorded in the electronic (e) case report forms (CRF). Treatment assignment will be notified by telephone with the central randomization center (IVRS) and confirmed by fax.

5.3 Randomization

Subjects will be randomized by the IVRS in a 1:1 ratio to 1 of 2 treatment groups: denosumab or placebo. Randomization will be stratified based on the following criteria at the time of study entry:

1. Breast cancer therapy / Lymph node (LN) status
    a. neo-adjuvant therapy / any LN status
    b. adjuvant therapy / LN negative (based on axillary LN dissection, or based on sentinel node [SN] status)
    c. adjuvant therapy / LN positive
2. Hormone receptor (estrogen receptor [ER]/ progesterone receptor [PR]) status
    a. ER and/or PR positive
    b. ER and PR negative
3. Human epidermal growth factor receptor 2 (HER-2) status
    a. HER-2 positive
    b. HER-2 negative
4. Age
    a. < 50
    b. ≥ 50
5. Geographic Region
    a. Japan
    b. Other

The randomization list will be generated and maintained by an Amgen Inc representative not involved in the conduct of the study. The subject, center personnel and all Amgen and Daiichi Sankyo Co., Ltd. study personnel and designees involved in the conduct of the study, will remain blinded to the randomized treatment assignment for investigational product, with the following exceptions:

- for analysis of the denosumab concentration levels, anti-denosumab antibody samples, and biomarker samples. Serum samples from those subjects who received denosumab will be identified by select unblinded Amgen individuals who will be directly involved with the analysis of those samples (ie**,** Amgen's Biological Sample Management, Pharmacokinetics, Clinical Immunology, and Hematology/ Oncology Research groups)
- for those circumstances, where the investigator deems it necessary to break the blind in order to provide appropriate medical treatment for the subject
- members of the external data monitoring committee (DMC) will have access to subject treatment assignments. To minimize potential introduction of bias, these individuals will not have any direct contact with the study personnel or subjects.

Refer to Section 10.4 and 11.2 for details on when and how the randomization code may be broken.

6. TREATMENT PROCEDURES

Denosumab and placebo will be considered the investigational products in this study. In addition, all subjects will be required to receive vitamin D and calcium supplementation at standard doses (at least 500 mg calcium and at least 400 IU of vitamin D; see Section 6.7), unless documented hypercalcemia develops on study; these medications will be referred to as supplements.

6.1 Investigational Product Dosage, Administration, and Schedule

Investigational product (denosumab 120 mg or matching placebo) will be administered by SC injection by a licensed healthcare professional after all other study visit procedures have been completed (except imaging). The first dose of investigational product must be administered within 8 days of randomization.

During the first approximate 6 months of treatment, investigational product will be administered Q4W (± 7 days). Investigational product may be administered Q3W to subjects receiving or scheduled to receive Q3W adjuvant/ neoadjuvant chemotherapy, to minimize patient clinic visits and enhance adherence to treatment. There must be at least a 3-week interval between administrations of investigational product.

During the subsequent 4½ years (approximately 54 months) of treatment, investigational product will be administered Q3M (ie, every 12 weeks ± 14 days). The total treatment duration will be 5 years (approximately 60 months).

The dosing schedule is described by a Schema at the end of the Protocol Synopsis. Refer to the Investigational Product Instruction Manual for information on the administration of investigational product.

6.2 Missed Doses

If any scheduled dose after study day 1 is delayed for more than 8 calendar days in the first approximate 6 months and more than 15 calendar days in the subsequent 4 ½ years from the scheduled visit date, then this will be considered a missed dose and recorded as such on the eCRF. The next dose is to be given on the next scheduled visit date. There must be at least a 3-week interval between scheduled administrations of investigational product.

6.3 Overdose

Neither the effects of overdose of denosumab nor an antidote to overdose are known. Subjects who have received higher than recommended doses must be carefully monitored for adverse events.

6.4 Dosage Adjustments

There will be no dose adjustments for the investigational product.

6.5 Dose Escalation and Dose Stopping Rules

There are no planned dose escalations in this study.

Administration of investigational product (denosumab or placebo) will be withheld for any subject who experiences a grade 3 or 4 adverse event per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 reported by the investigator as related to investigational product, **atypical femoral fracture (AFF),** or osteonecrosis of the jaw (ONJ)**,** as determined by the investigator or by an independent expert panel. Re-exposure to investigational product may occur only when the event resolves to grade 1 or less or the subject's baseline and if the investigator and the sponsor agree subject safety will not be compromised.

Administration of investigational product (denosumab or placebo) will also be withheld 30 days prior to any elective invasive oral/ dental procedure. Investigational product administration will be withheld until documented evidence of complete mucosal healing following any invasive oral/ dental procedure.

6.6 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.8.

Chemotherapy, hormonal therapy, biological therapy, surgery or radiation therapy for breast cancer is allowed during study treatment. All treatment for breast cancer must be recorded on the eCRF.

All concomitant medications, including over-the-counter products, administered while the subject is enrolled in the study must be recorded on the eCRF.

6.7 Supplements

All subjects will 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) develops on study. Due to differences in regional availability, a dosage form of vitamin D that gives an equivalent of at least approximately 400 IU daily may be given. All supplements must be recorded on the eCRF.

6.8 Proscribed Therapy During the Study Period

Intravenous bisphosphonates must not be administered, while subjects are on study treatment. Likewise, oral bisphosphonates must not be administered for the adjuvant/neoadjuvant treatment of breast cancer, while subjects are on study treatment.

Denosumab available through commercial sources (eg, XGEVA™, Prolia®) must not be administered while subjects are on study treatment.

In addition, use of any unapproved (ie, no marketing authorization has been granted) investigational product (other than denosumab, as specified in the study protocol) or investigational device is not allowed until after all EOTP assessments are completed.

Subjects who receive a treatment regimen of IV bisphosphonates, oral bisphosphonates for the adjuvant/neoadjuvant treatment of breast cancer, or commercial denosumab, or any unapproved investigational product(s) or investigational device(s) during study treatment must be discontinued from further administration of investigational products, but will continue with all other study assessments without further investigational product administration per the schedule of assessments.

Therapy to be Avoided During the Study Period

Use of bone-targeted treatment (other than supplemental calcium and vitamin D, and investigational product) should be avoided while subjects are on study treatment, unless medically indicated (eg, oral bisphosphonates for the treatment of osteoporosis on study). Each use of bone-targeted treatment while subjects are on study treatment must be recorded on the eCRF.

Invasive oral/ dental procedures should be avoided if possible. See Section 6.5 for investigational product dose withholding prior to and following invasive oral/ dental procedures.

7. STUDY PROCEDURES

7.1 General Study Procedures

A written informed consent must be obtained before any study assessments or procedures are performed. All on-study assessments (except imaging) must be completed before investigational product administration. Refer to the schedule of assessments (Appendix A) for the description of procedures required during screening and on study.

7.1.1 Screening Procedures

Screening samples (ie, serum calcium, albumin, and pregnancy test) will be submitted to the central laboratory for analysis and results must be available at the time of randomization.

- Screening labs and (for subjects with reproductive potential) a pregnancy test must be completed no more than 14 days before the day of randomization. If a pregnancy test result will be more than 14 days old at the time of randomization, then the test must be repeated
  - If screening samples were collected within 3 days prior to study day 1, then the laboratory assessments performed in screening do not need to be repeated on study day 1

Procedures that have been performed prior to screening as part of routine clinical care are not considered study-specific procedures. However, the following procedures may be used for screening purposes, if conducted according to the timelines for screening procedures:

- Radiologic disease assessments (mammography, full body radioisotope bone scan, and computed tomography [CT] or magnetic resonance imaging [MRI]), must be performed within 24 weeks before the day of randomization. The same imaging modality and technique should be used throughout the study (see Section 7.2.9).
- All other assessments/ procedures must be completed no more than 28 days before the day of randomization.

The subject's complete medical history will be collected during screening and must date back to at least the original diagnosis of breast cancer, or 5 years, whichever is longer. If a subject is referred to the study center, copies of all applicable reports and histological or cytological evidence confirming the diagnosis must be provided to the study center before randomization.

Refer to the schedule of assessments (Appendix A) for the description of procedures required during screening. Study day 1 (day of first dose of investigational product) must be planned within 8 calendar days from randomization.

7.1.2 On-Study Procedures

Refer to the schedule of assessments (Appendix A) for the description of procedures required on study.

7.1.2.1 Study Treatment

Study treatment (investigational product: denosumab at a dose of 120 mg or matching placebo) will be administered by a licensed healthcare professional SC Q4W (± 7 days, at least 3 weeks apart; see Section 6.1) for approximately 6 months, followed by investigational product SC Q3M (ie, every 12 weeks ± 14 days) for 4½ years (approximately 54 months), for a total treatment duration of 5 years (approximately 60 months), or until documented evidence of bone metastasis (per central imaging analysis or biopsy), whichever is earlier. During the first approximate 6 months of treatment, investigational product may be administered Q3W to subjects receiving or scheduled to receive Q3W adjuvant/neoadjuvant chemotherapy (see Section 6.1). There must be at least a 3-week interval between administrations of investigational product.

7.1.2.2 Study Visits and Assessments

Study visits will occur as required for treatment administration and study assessments per the schedule of assessments (Appendix A): Q4W (± 7 days, at least 3 weeks apart) for approximately 6 months, then Q3M (ie, every 12 weeks ± 14 days) for approximately 54 months. See Section 7.2 for Specific Study Procedures.

Any missed visits or assessments that are not conducted must be reported as such on the respective eCRFs. See Section 6.2 for a definition of Missed Doses.

7.1.2.3 Early Withdrawal From Blinded Investigational Product

Subjects, who discontinue investigational product administration (ie, withdraw partial consent), will continue all other on-study procedures without investigational product administration according to the schedule of assessments (Appendix A) for the remainder of the treatment phase (approximately 60 months from study day 1) before entering follow-up.

Subjects, who discontinue investigational product administration and who also withdraw partial consent to continue on-study procedures after they discontinued investigational product, will terminate the treatment phase, complete the EOTP visit, and proceed with follow-up procedures as outlined in Section 7.1.4.

7.1.3 End of Treatment Phase (EOTP)

The EOTP visit will be completed per Schedule of Assessments (Appendix A; ± 14 days), or at any time once an individual subject discontinues study participation (eg, full consent withdrawal) 4 weeks **(**+ 7 days**)** after the last dose of investigational product. If more than 4 weeks have elapsed since the last dose when a subject discontinues study participation, the EOTP visit will be conducted as soon as possible.

All EOTP assessments must be completed (unless done within the prior 4 weeks), except imaging assessments, which do not need to be repeated if completed within the prior 6 months (ie**,** 24 weeks).

7.1.4 Follow-up Procedures

After completing the treatment phase of the study, subjects will **then enter LTFU for approximately 5 years (60 months) following the EOTP visit. The study requirements during LTFU are different before and after primary analysis data cut-off date and are detailed in Section 7.1.4.1 (before primary analysis data cut-off date) and Section 7.1.4.2 (after primary analysis data cut-off date).**

7.1.4.1 LTFU Requirements Prior to the Primary Analysis Data Cut-off Date

All subjects (including subjects with documented evidence of bone metastasis) should be followed by clinic visit or telephone contact every 3 months (every 12 weeks ± 14 days) for approximately 6 months (ie, first 2 visits of LTFU following EOTP).

- **The following assessments are required:**
  - **clinical fractures/SREs**
  - **hypercalcemia of malignancy**
  - **breast cancer therapy**
  - **concomitant medications**
  - **patient-reported outcomes (BPI-SF, EQ-5D)**
  - **disease recurrence status (until documented evidence of bone metastasis [per central imaging analysis or biopsy]). Not required for subjects with documented evidence of bone metastasis**
  - **survival**

All subjects without documented evidence of bone metastasis: following the completion of the initial 6 month LTFU period, subjects should be followed by clinic visit or telephone contact every 3 months (every 12 weeks ± 14 days).

- **The following assessments are required:**
  - **clinical fractures/SREs**
  - **hypercalcemia**
  - **disease recurrence status (until documented evidence of bone metastasis [per central imaging analysis or biopsy])**
  - **survival**

Imaging assessments will continue during **LTFU** per the schedule of assessments (Appendix A), until documented evidence of disease recurrence in the bone (per central imaging analysis or biopsy). See Section 7.2.9 for details.

Biomarker samples will be taken at the time of disease recurrence (including both first disease recurrence, and first disease recurrence in the bone, if applicable).

Subjects <u>with</u> documented evidence of bone metastasis including subjects whose bone metastasis is confirmed after the initial 6 month (per central imaging analysis or biopsy): following the completion of the initial 6 month LTFU period, subjects should be followed by clinic visit or telephone contact every 6 months (± 1 month).

- **The following assessments are required:**
  - **SREs**
  - **hypercalcemia**
  - **survival**

7.1.4.2 LTFU Requirements After the Primary Analysis Data Cut-off Date

Following the primary analysis data cut-off date, all subjects should complete the EOTP visit and will be followed by clinic visit or telephone contact every 6 months (± 1 month) for survival only. All scheduled imaging and all other assessments (except survival) will cease after the primary analysis data cut-off date.

7.2 Specific Study Procedures

7.2.1 Medical History

The subject's medical history will be obtained prior to randomization and recorded on the eCRF. Detailed history of breast cancer (including the date and staging of original diagnosis, tumor histology, grade, hormone receptor [ER/PR] status, HER-2/neu status) will be obtained. Refer to Appendix D, Breast Cancer Staging and Grading, for details.

7.2.2 Treatment History

The subject's history of anti-neoplastic treatment and radiotherapy for breast cancer will be collected on the eCRF.

7.2.3 Physical Examination

Each physical examination will include assessment of Eastern Cooperative Oncology Group (ECOG) performance status, height (during screening only), weight, and vital signs (blood pressure, respiration rate, pulse, and temperature). Refer to Appendix C for ECOG performance status criteria.

7.2.4 Oral Examination

A visual examination of the oral cavity, including teeth, mucosa, and gums will be conducted by the investigator or designated licensed healthcare professional, at screening to establish baseline oral health conditions and approximately every 6 months thereafter, to identify and document any new abnormalities or changes in pre-existing conditions.

If any new abnormalities or changes in pre-existing conditions are identified, additional information may be requested.

7.2.5 Adverse Event Collection

Adverse events must be assessed and documented at each scheduled clinic visit. Subjects must be followed for adverse events until the End of the Treatment Phase (EOTP), or for 30 days after the last dose of investigational product for subjects who discontinue investigational product before the EOTP. See Section 9 for details. Exceptions are hypercalcemia of malignancy, clinical fractures, and SREs, which will **continue to** be **collected during LTFU prior to primary analysis data cut-off date** (see Sections 7.2.5.1 and 7.2.6).

7.2.5.1 Hypercalcemia of Malignancy

Clinical events of hypercalcemia of malignancy will be collected on the eCRF throughout the study and during **LTFU prior to primary analysis data cut-off date**.
Hypercalcemia of Malignancy is defined in this study as a serum calcium value (albumin-adjusted if necessary) of CTCAE version 3.0 grade 2 or greater (ie, > 11.5 mg/dL; > 2.9 mmol/L; ionized calcium > 1.5 mmol/L).

7.2.6 Clinical Fracture and Skeletal-related Event Collection

Skeletal-related events (SREs) are defined as any pathologic fracture (vertebral or non-vertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression following the development of bone metastasis.

Pathologic fractures are those bone fractures that occur spontaneously or result from trivial trauma. Vertebral fractures will include compression fractures.

Surgery to bone includes procedures to set or stabilize a fracture or to prevent an imminent fracture or spinal cord compression.

Radiation therapy to bone includes radiation for pain control (including use of radioisotopes), to treat or prevent pathologic fractures, or to treat or prevent spinal cord compression.

Spinal cord compression events must be confirmed using appropriate radiographic imaging (eg, MRI, CT, or myelogram).

Information about any new clinical fractures **(prior to the development of bone metastasis)** or SREs will be assessed and documented on the eCRF at each scheduled clinic visit and during **LTFU prior to primary analysis data cut-off date**. Copies of all radiographic assessments performed to diagnose clinical fractures and SREs must be submitted to the central imaging vendor. Copies of all screening and on-study radiology, surgery, or pathology reports should be kept in the subject's records regardless if corresponding radiographs (or equivalent) are available.

Radiographic assessments for clinical fractures and SREs collected after primary analysis data cut-off date will not be submitted to the central imaging vendor.

7.2.7 Concomitant Medication Collection

Information regarding the type and timing of concomitant medications, including any analgesic medication, and treatments will be collected at the time points specified in the schedule of assessments (Appendix A). Calcium and vitamin D supplements must be recorded on the Calcium and vitamin D medication eCRF.

7.2.8 Patient Reported Outcomes

Patient reported outcomes (Brief Pain Inventory- Short Form [BPI-SF; see Appendix H], and EuroQol-5 Dimension Health Utility Questionnaire [EQ-5D; see Appendix I]) will be completed before any study procedures are performed (including physical exam, vital

signs, laboratory assessments, imaging, and treatment administration) at the time points specified in the schedule of assessments (Appendix A).

7.2.8.1 Brief Pain Inventory - Short Form (BPI-SF)

The BPI-SF (see Appendix H) is a questionnaire specifically designed to assess pain in cancer. The BPI-SF captures information on the intensity of pain (pain severity) as well as the degree to which pain interferes with function (pain interference). Evidence for reliability and validity of the BPI-SF has been well documented in cancer patients (Cleeland CS, 1991).

7.2.8.2 EuroQol-5 Dimensions (EQ-5D)

The EQ-5D (see Appendix I) is a standardized instrument developed by the EuroQol Group for use as a generic, preference-based measure of health outcome. It is applicable to a wide range of health conditions and treatments and provides a simple descriptive profile and a single index value for health status (EuroQol Group, 1990, 2009). The EQ-5D is a 5-item self-reported measure of functioning and well-being, which assesses 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension comprises 3 levels (no problems, some/moderate problems, extreme problems). A unique EQ-5D health state is defined by combining 1 level from each of the 5 dimensions. This questionnaire also records the respondent's self-rated health status on a vertical graduated (0-100) visual analogue scale. Responses to the 5 items will also be converted to a weighted health state index (utility score) based on values derived from general population samples. The EQ-5D is recommended for use in cost-effectiveness analyses commonly employed in health technology assessments by the Washington Panel on Cost Effectiveness in Health and Medicine (Gold, 1996).

7.2.9 Imaging Assessments

7.2.9.1 Disease Assessments (Mammography, Bone Scan, CT/MRI)

The following imaging assessments must be present at screening (performed within 24 weeks prior to randomization), to assess disease extent: mammography (except after total mastectomy, in which case only the remaining breast [if applicable] must be imaged), full body skeletal scintigraphy ("full body radioisotope bone scan" or 'bone scan'), as well as computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and all other suspected sites of disease. For subjects with historical mammograms, the historical images obtained most recently (prior to the screening time point) should be submitted to central imaging vendor, if available).

On study and during follow-up, imaging will consist of mammography (except after total mastectomy, in which case only the remaining breast [if applicable] must be imaged), full body radioisotope bone scans, and CT or MRI imaging of the chest, abdomen, and all other known or suspected sites of disease, at the end of year 1 (ie, 52 weeks from study day 1), yearly thereafter (ie, at the end of year 2, 3 etc.), as clinically indicated, to confirm disease recurrence, and at the EOTP visit (see Schedule of Assessments). All scheduled on-study imaging must be performed within ± 6 weeks of the protocol-specified time point, unless performed within the previous 6 months. **All scheduled imaging will cease after the primary analysis data cut-off date.** Extra-osseous disease assessments (mammography, CT or MRI of the chest, abdomen, and all other known or suspected sites of disease) will cease upon documented disease recurrence (per central imaging analysis, biopsy, or cytology). All scheduled imaging will cease upon documented disease recurrence in the bone (per central imaging analysis or biopsy). The imaging modality selected should remain the same throughout the study.

Any abnormal bone scan (per central imaging analysis) must be confirmed within 4 weeks of investigative site notification using X-ray, CT, MRI or biopsy evidence of lesions consistent with bone metastasis for all areas identified on the bone scan, until documented disease recurrence in the bone (per central imaging analysis or biopsy). See Appendix E for details.

Re-staging will be completed within 4 weeks of either site notification by the central imaging vendor of the subject's first instance of disease recurrence, or histological/cytological confirmation of the subject's first instance of disease recurrence. For the purposes of this protocol, re-staging requires the following imaging to be completed:

- Full body radioisotope bone scan
- CT or MRI of the chest, abdomen, and all other suspected sites of disease
- Bilateral Mammography

In the case of total mastectomy, only mammography of the remaining breast (if applicable) is required. Applicable bone scans, CTs/MRIs, and mammography performed as early as 12 weeks prior to the procedure (imaging, biopsy, or cytology) that confirms disease recurrence will satisfy the restaging requirements, and therefore would not need to be repeated.

All scheduled and unscheduled radiological imaging and pathological assessments will be reviewed locally and documented by the investigator on the eCRF. Copies of all

scheduled and unscheduled screening and on-study radiographic assessments performed to monitor or diagnose breast cancer must be submitted to the central imaging vendor. This includes any such images deemed to be negative by the local radiologist and any standard-of-care or routine disease monitoring images performed even if not specified by protocol. Copies of all screening and on-study radiology, surgery, or pathology reports should be kept in the subject's records regardless if corresponding radiographs (or equivalent) are available. Assessments for disease recurrence will be performed according to the Definitions and Criteria for Diagnosis of Breast Cancer Recurrence outlined in Appendix E.

7.2.9.2 Breast Density Assessments (Mammography)

Breast density will be measured by the central imaging vendor on the annual mammograms collected for the purpose of disease assessments, as outlined above (Section 7.2.9.1). No additional imaging will be required.

7.2.10 Laboratory Assessments

Serum, blood and urine samples will be submitted to the central laboratory for analysis. Amgen Inc. or its designee will be responsible for analyzing all samples. Laboratory assessments should be performed on the day of the scheduled visit, or within 3 days prior to the visit. All central laboratory values will be electronically transferred from the laboratory to the Amgen clinical database. Specific details can be found in the data transfer plan for the central laboratory.

7.2.10.1 Blood Assessments

All blood samples will be obtained by venipuncture before investigational product administration. The average volume of blood drawn per visit will be approximately 2.5 to 30 mL. Blood will be obtained for the assessments outlined in Table 1 at the time points specified in the schedule of assessments (Appendix A). The date and time of blood collection will be recorded in the subject's medical records.

Table 1. Serum, Blood and Urine Sample Analyte Listing (Central Labs)

Serum Chemistry	Other	At selected sites only
Albumin Calcium or Albumin-adjusted Calcium	Pregnancy Test Anti-denosumab antibodies (binding and neutralizing)	Denosumab concentration levels (120 subjects at selected sites)
Magnesium (Mg)	Bone Specific Alkaline Phosphatase (BSAP)	
Phosphorus (P)	Blood biomarkers	
Vitamin D	Urinary C-telopeptide (αCTX)	
Hematology	Urinary N-telopeptide (uNTx)	
Complete blood cell count (CBC) and differential	Urine creatinine (for correcting raw uNTx)	

To maintain the integrity of the study blind, Visit 2 and Visit 3 laboratory results for calcium (or albumin-adjusted calcium, if applicable) will not be reported to investigative sites. To ensure adequate safety oversight, if there is a change of these analytes to CTCAE grade 3 or greater, the central laboratory will notify both the investigative site and Amgen Inc of the absolute analyte value. All on-study bone specific alkaline phosphatase (BSAP) results will be blinded to investigative sites.

Denosumab PK: Samples for serum denosumab concentration levels will be obtained on a subset of approximately 120 subjects at baseline (prior to administration of investigational product on study day 1), and on study as outlined in the schedule of assessments (Appendix A), at selected sites.

The centers that will participate in this part of the study will be determined at the time of site selection, on the basis of center interest, site ability to obtain and process serum denosumab concentration samples, and recruitment capacity. A competitive enrollment strategy will be used. Serum levels for denosumab will be obtained in randomized subjects at these centers until approximately 120 subjects have been enrolled into the PK portion of the trial (optional for subjects).

Anti-denosumab antibodies: Serum for anti-denosumab antibody assay will be collected at baseline (prior to administration of the investigational products on study day 1) **and** on study as outlined in the schedule of assessments (Appendix A).

Blood biomarkers and **Bone Specific Alkaline Phosphatase (BSAP)**: Blood for biomarker assessments and BSAP will be obtained at baseline (prior to administration of the investigational products on study day 1), on study as outlined in the schedule of

assessments (Appendix A), and upon disease recurrence (including both first disease recurrence, and first disease recurrence in the bone, if applicable).

7.2.10.2 Urine Assessments

All urine samples will be collected prior to investigational product administration. Urine samples will be collected for urinary N-telopeptide (uNTx) and alpha C-telopeptide (αCTX). Urine analytes will include creatinine and raw N-telopeptide (NTx). Amgen Inc. or its designee will perform these assays and will measure urine creatinine.

The uNTx will be corrected for urine creatinine by generating a ratio. Using the uNTx as reported in units of nM and urine creatinine in units of mg/dL, the creatinine measurement will be multiplied by 0.0884, and used to generate the corrected ratio. The resulting equation will be: uNTx/Cr (nM BCE/mM) = uNTx/(Cr*0.0884).

Urine will be obtained at baseline (prior to administration of investigational product on study day 1), on study as outlined in the schedule of assessments (Appendix A), and upon disease recurrence (including both first disease recurrence, and first disease recurrence in the bone, if applicable).

Urine collection instructions

A urine sample must be collected from subjects, preferably after the first void in the morning. It is recommended that urine samples be collected in the clinic, if feasible. If the subject is to collect the urine sample at home, she will need to be provided with containers for sample collection and for transporting the sample to the site on the day of collection. Subject instructions will be provided on how and when to collect the sample, recording the time of collection, and storing the sample (refrigerated) until it is brought to the study site for processing.

7.2.10.3 Tumor Samples

Archived paraffin-embedded formalin-fixed breast tumor tissue block(s) (surgical specimens or biopsy samples obtained as part of routine clinical care) ascertained to contain tumor cells, along with copies of all corresponding pathology reports, will be submitted to the central laboratory at screening, and/or as they become available as part of routine clinical care. In lieu of a whole block, approximately 20 charged, unstained slides may be sent to the central laboratory (see below paragraphs for instructions).

It is important that adequate samples are sent to the central laboratory as soon as possible, to allow the central laboratory time to evaluate the samples, and to ask for additional samples if the initial samples are not appropriate. The tumor block should be

carefully selected by a pathologist or a skilled experienced histology associate to include generous tumor tissue, using the pathology report as a guide. The block with the most tumor should be selected for submission or preparing slides.

If tumor tissue sections on slides are submitted to the central laboratory for this study, then the following specifications for the slides are preferred and requested: ~20 slices, 5 micron thick, will be cut from the same block onto charged slides. The slides will be labeled by etching or using an indelible histology marker with the block ID (block number) to match the pathology report. In cases where the adequacy of a tissue specimen is not clear, it is acceptable to submit more than one block or series of slide replicates containing tumor tissue. The pathology report must accompany the submitted specimen(s), or the submission may not be considered complete.

The subject's personal and confidential information (eg, name, social security number) will be blacked out on the pathology report in order to protect the subject's identity. However, the subject ID number will be written on the report. The specimen collection date, and block ID (numbers) must be visible and legible.

No additional invasive procedures for collection of tumor tissue are required for this study.

7.3 Biomarker Development and Pharmacogenetic Studies

7.3.1 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage disease, assess tumor growth and metastasis, and/or predict disease response to an intervention such as denosumab. These investigations may be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease recurrence. Biomarker development may be pursued by use of advanced biochemical analyses, such as proteomic methods or ribonucleic acid transcript profiling.

An exploratory goal of this study is to identify biomarkers that may enhance our understanding of breast cancer and/or determine how subjects respond (positively or negatively) to denosumab. For example, for pharmacodynamic evaluation following treatment with denosumab, levels in the blood of factors, which can influence tumor progression, such as vascular endothelial growth factor (VEGF) or basic fibroblast growth

factor (bFGF) are of interest. Expression of genes that are involved in the targeted pathways in archived tumor tissue may be evaluated to determine relationships with treatment-related responses. This may include evaluation of RANK, OPG and/or RANKL expression as well as biochemical markers which may indicate an active RANK/RANKL pathway.

When adequate tumor tissue is available, analyses in tumor tissue of tumor specific mutations or epigenetic changes in oncogenes or pathways related to the targeted pathway may be performed (eg, OPG, RANK, or RANKL). Hereditary elements will not be analyzed, unless the optional pharmacogenetic consent has been provided (see Section 7.3.2).

7.3.2 Pharmacogenetic Studies (Optional)

If the subject signs the additional optional informed consent (Pharmacogenetic Consent), deoxyribonucleic acid (DNA) may be used for optional, exploratory pharmacogenetic analyses. These optional analyses focus on inherited genetic variations, to evaluate their possible correlation to breast cancer and/or responsiveness to denosumab. The goals of these optional studies include the use of genetic markers to help in the investigation of breast cancer and/or to identify persons who may have the best possible response to denosumab. No additional blood or tumor samples will be collected for this part of the study. However for those subjects who consent to these optional studies, DNA extracted from blood samples collected for biomarker development may be analyzed.

7.3.3 Sample Storage and Destruction

The blood and tumor samples and any other components from the cells collected on study may be stored for up to 20 years (depending on local requirements) to research scientific questions related to breast cancer and/or denosumab. The subject retains the right to have the sample material destroyed at any time by contacting the principal investigator (or equivalent role in Japan). The sponsor will be the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the research subject through the principal investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). Following the request from a research subject, the principal investigator (or equivalent role in Japan) will provide the sponsor with the required study and subject numbers so that any remaining blood and tumor samples and

any other components from the cells collected on study can be located and destroyed. If a commercial product is developed from this research project, the sponsor will own the commercial product. The subject will have no commercial rights to such product and will have no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 12.4 for subject confidentiality.

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

Subjects have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject the most appropriate way to withdraw to ensure the subject's health.

Withdrawal of partial consent means that the subject does not wish to receive investigational product any longer but is still willing to collaborate in providing further data by continuing on study (eg, participate in all subsequent study visits or procedures). Subjects may decline to continue receiving investigational product at any time during the study. These subjects, as well as those who have stopped receiving investigational product for other reasons (eg, investigator or sponsor concern) will continue the schedule of study assessments.

Reasons for removal from investigational product might include (but are not limited to):

- withdrawal of partial or full consent
- documented evidence of bone metastasis (per central imaging analysis or biopsy, or [open-label treatment phase only] per investigator report)
- administrative decision by the investigator or Amgen and (for Japanese sites only) Daiichi Sankyo Co., Ltd.
- pregnancy (report on Pregnancy Notification Worksheet, see Appendix F)
- ineligibility
- significant protocol deviation
- patient noncompliance
- adverse event (report on adverse event eCRF)
- administration of IV bisphosphonates
- administration of oral bisphosphonates for the adjuvant/neoadjuvant treatment of breast cancer

Extra-osseous disease recurrence does not necessarily indicate failure of bone-targeted treatment. Therefore, every effort should be made to continue the subject on investigational product until documented disease recurrence in the bone (per central imaging analysis or biopsy).

Subjects, for whom ineligibility is determined, may be removed from study.

8.2 Replacement of Subjects

Subjects will not be replaced.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definitions

9.1.1 Adverse Events

An adverse event is defined in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.” (ICH E6:1.2)

The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject’s medical record.

This definition of adverse events is broadened in this study to include any such occurrence (eg, sign, symptom, or diagnosis) or worsening of a pre-existing medical condition from the time that a subject has signed informed consent to the time of randomization to or initiation of investigational product. Worsening indicates that the pre-existing medical condition **or underlying disease** (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, **and/**or duration **more than would be expected, and/or has** an association with **a** significantly worse outcome **than expected**.

If infections occur, microbiological investigations (eg**,** cultures) should be performed as clinically feasible to identify a causative organism, and specific data should be reported.

Recurrence of breast cancer should not be reported as an adverse event. However, any specific symptoms or sequelae of the disease recurrence (eg, organ failure, respiratory distress, etc) will be considered adverse events and will be captured on the eCRF.

Interventions for pretreatment conditions (eg, elective surgery) or**,** medical procedures that were planned before study enrollment**,** are <u>not</u> considered adverse events.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a **clinically significant** change from **the subject's baseline** values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events. **Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event. The investigator is expected to follow reported adverse events until stabilization or reversibility.**

9.1.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that **meets at least 1 of the following criteria:**

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other significant medical hazard

A hospitalization meeting the regulatory definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility.

Any adverse event that does not meet one of the definitions of serious (eg, emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the "other significant medical hazard" criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasias**, drug-induced liver injury, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention**.

Elective hospitalizations (eg, for the routine administration of radiotherapy, chemotherapy, or therapeutic blood products) are not considered Serious Adverse Events. However, prolongation of hospitalization or readmission after the subject has been discharged post-radiotherapy or chemotherapy will be considered a Serious Adverse Event.

9.1.3 Adjudication Process for Suspected Osteonecrosis of the Jaw and Suspected Atypical Femoral Fracture Adverse Events

All subjects with an oral adverse event suspicious of osteonecrosis of the jaw (ONJ) should be examined by a dentist or other qualified oral specialist (eg, oral surgeon). All subjects presenting with new or unusual thigh, hip, or groin pain should be evaluated for a suspected adverse event of AFF.

Adverse events reported as ONJ or AFF as well as adverse events identified by Amgen as potentially representing ONJ or AFF will be reviewed by an independent adjudication panel of experts to determine whether the pre-defined criteria for ONJ or AFF are met. Amgen will request the investigating site to provide all available source documents surrounding that event to be reviewed by the blinded adjudication committee.

All countries (except Japan): If an event is adjudicated positive for ONJ, the investigator will be notified of the adjudication decision and the event will be reported to regulatory agencies and study investigators in an expedited manner.

Japan only: If an event is adjudicated positive for ONJ, the investigator will be notified of the adjudication decision and the event will be reported to regulatory agencies and study investigators in accordance with Japanese regulation.

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

The investigator is responsible for ensuring that all adverse events (as defined in Section 9.1 and as further specified below) observed by the investigator or reported by subjects are collected and recorded in the subjects' medical records, in the eCRF. These adverse events will include all non-serious adverse events (as defined in Section 9.1.1) that occur after randomization to investigational product until the EOTP, or for 30 days after the last dose of investigational product for subjects who discontinue investigational product before the EOTP.

The following adverse event attributes must be assigned by the investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); dates of onset and resolution; severity; assessment of relatedness to investigational product; and action taken.

If applicable, the relationship of the adverse event to the investigational product will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by the investigational product?" The investigator should respond to this question with either Yes or No.

If the adverse event occurred before randomization to investigational product, the relationship of the adverse event to study screening is to be assessed by means of a similar question: "Is there a reasonable possibility that the event may have occurred because of study screening?" The investigator should respond to this question with either Yes or No. If the answer is Yes, record what part of the study screening is suspected.

The NCI CTCAE v3.0 severity grading scale will be used in this study (see Appendix B).

Medically significant adverse events considered related to the investigational product by the investigator or the sponsor will be followed until resolved or considered stable.

It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the EOTP, or for 30 days after the last dose of investigational product for subjects who discontinue investigational product before the EOTP**, are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Adverse Event CRF.**

All serious adverse events that occur after the subject has signed the informed consent form must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable electronic Serious Adverse Event (eSAE) eCRF. If the electronic data capture (EDC) system is unavailable to the site staff to report the Serious Adverse Event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the Investigator's knowledge of the event. See Appendix G for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form. **For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSAE Contingency Report Form, the data must be entered into the EDC system when the system is available again.**

The investigator must assess whether the serious adverse event is possibly related to the investigational product and/or other protocol-required therapies. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product? Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. **If specifically requested, t**he Investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable eCRF (eg, Adverse Event Summary eCRF).

To comply with local or regional serious adverse event reporting regulations, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded before submission to regulatory authorities by Amgen Global Safety. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions (SUSARs) as required to regulatory authorities, investigators/ institutions and ethics committees in compliance with all applicable regulatory requirements and

ICH GCP guidelines.

Japan only: Daiichi Sankyo will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, Investigators/institutions, and IRBs/ECs in compliance with all reporting requirements according to local regulations and good clinical practice.

If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be included in the initial or follow-up Serious Adverse Event Report Form as well as the End of Investigational Product Administration eCRF and the EOTP eCRF.

The investigator should notify the appropriate IRB or ethics committee of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

9.2.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of following the protocol-required reporting or after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs while the subject is taking protocol-required therapies report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, **i**nvestigators should **report** pregnancies that occur **through 5 months** after the last dose of protocol-required therapies.

The pregnancy should be reported to Amgen **G**lobal **Patient Safety** within **24 hours** of the **investigator's knowledge of the event** of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix F). **Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.**

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, **i**nvestigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 5 months after the end of treatment.

Any lactation case should be reported to Amgen **G**lobal **Patient Safety** within **24 hours** of the **investigator's knowledge of event**. Report a lactation case on the Lactation Notification Worksheet (Appendix K).

10. STATISTICAL CONSIDERATIONS

10.1 Study Design

This is an international phase 3 randomized double-blind placebo-controlled study in women with early-stage (stage II or III) breast cancer at high risk of disease recurrence. Approximately 4,500 subjects will be randomized in a 1:1 ratio to receive denosumab 120 mg or matching placebo. Randomization will be stratified based on the following criteria at the time of study entry:

1. Breast cancer therapy / Lymph node (LN) status
    a. neo-adjuvant therapy / any LN status
    b. adjuvant therapy / LN negative (based on axillary LN dissection, or based on SN status)
    c. adjuvant therapy / LN positive
2. Hormone receptor (ER/ PR) status
    a. ER and/or PR positive
    b. ER and PR negative

3. Human epidermal growth factor receptor 2 (HER-2) status
    a. HER-2 positive
    b. HER-2 negative
4. Age
    a. < 50
    b. ≥ 50
5. Geographic Region
    a. Japan
    b. Other

An external DMC will monitor the study and conduct 1 interim analysis of efficacy. Refer to Section 10.5 for details.

The primary analysis will be conducted after all enrolled subjects have had the opportunity to complete 5 years of treatment from study day 1. Refer to Section 3.1 for details on the study design, and to the end of the Protocol Synopsis section for the Study Schema.

10.2 Study Endpoints, Subsets, and Covariates

10.2.1 Study Endpoints

Primary Endpoint

- Bone metastasis-free survival (BMFS)

Secondary Endpoints

- Disease-free survival (DFS; determined by the time from randomization to the first observation of disease recurrence or death from any cause) in the full study population
- DFS in the postmenopausal subset
- Overall survival (OS)
- Distant recurrence-free survival (DRFS)

Safety Endpoints

- Subject incidence of treatment-emergent adverse events
- Changes in laboratory values
- Subject incidence of anti-denosumab neutralizing antibody formation

Exploratory Endpoints

- Time to first bone metastasis (excluding deaths)
- Time to bone metastasis as site of first recurrence
- Time to disease recurrence (TTR)
- Time to distant recurrence
- Time to first on-study fracture (vertebral or non-vertebral fracture)

- Time to first on-study SRE (following the development of bone metastasis)
- Time to first on-study SRE or hypercalcemia (following the development of bone metastasis)
- Time to first on-study symptomatic bone metastasis
- BPI-SF 'worst' pain score
- BPI-SF pain severity and pain interference scales
- EQ-5D health index scores
- Analgesic use
- Breast density
- Pathological variables in tumor tissue from neoadjuvant subjects after surgery
- Pharmacokinetics
  - Serum trough levels of denosumab
- Pharmacodynamic response
  - Levels and dynamics of bone turnover markers and potential other pharmacodynamic markers
- Biochemical levels and abundance of drug targets in blood and/or tumor tissue, and correlate with treatment outcomes
- Association of tumor genetic variations in cancer genes, drug/pathway target genes, and/or other biomarker genes with treatment outcomes
- Analysis of genetic variations in cancer genes, drug/pathway target genes, and/or other biomarker genes, and correlate with treatment outcomes (optional; requires separate informed consent)

10.2.2 Study Subsets

10.2.2.1 Full Analysis Set

The Full Analysis Set (FAS) is defined as all subjects who are randomized to the study. This analysis set is the primary analysis set for efficacy endpoints.

10.2.2.2 Per Protocol Analysis Set

The Per Protocol Analysis Set is defined as all randomized subjects with a protocol-defined diagnosis, no major protocol violations, and who received at least one dose of investigational product. The major protocol violations will be defined in the Statistical Analysis Plan (SAP).

10.2.2.3 Safety Analysis Set

The Safety Analysis Set includes all randomized subjects who received at least 1 dose of investigational product. Subjects will be analyzed according to the actual treatment received, irrespective of the randomized treatment. All safety analyses will be performed using this analysis set.

10.2.2.4 Pharmacokinetic Analysis Set

The PK Analysis Set includes all subjects in the FAS who undergo PK blood sampling during the study and who have received at least one dose of denosumab. Subjects that are determined to have deviations in study-related procedures that may affect the quality of the PK data may be removed from the PK analysis set.

10.2.2.5 Biomarker Analysis Set

The Biomarker Analysis Set includes all subjects in the FAS, who undergo biomarker sampling during the study. Subjects that are determined to have deviations in study-related procedures that may affect the quality of the biomarker data may be removed from the biomarker analysis set.

10.2.3 Covariates

Covariates to define subsets include breast cancer therapy / lymph node status (neo-adjuvant therapy / any LN status vs adjuvant therapy / LN negative [based on axillary LN dissection, or based on sentinel node {SN} status] vs adjuvant therapy / LN positive), hormone receptor (ER/PR) status (ER and/or PR positive vs ER and PR negative), human epidermal growth factor receptor 2 (HER-2) status (positive vs negative), age (< 50 vs ≥ 50), and region (Japan vs Other). These covariates will be used to stratify subjects into treatment arms (denosumab or matching placebo) as part of the randomization process, and in the primary analysis as described in Section 10.6, Planned Methods of Analysis.

The relationship of the following covariates to the primary and secondary efficacy endpoints may be explored:

- Breast cancer therapy / Lymph node status
- Hormone receptor (ER/PR) status
- HER-2 status
- Age
- Menopausal status
- Breast cancer stage
- Primary tumor size
- Lymph node status
- Breast cancer histopathologic grade
- Region

Other covariates reported in the literature or from other ongoing Amgen studies may be considered in the analysis as appropriate at the time of analysis.

10.3 Sample Size Considerations

The sample size calculation is based on the primary endpoint, BMFS, and is estimated using EAST **6.4**. Estimates of the event rates for BMFS and DFS for the target population are based on (Colleoni et al., 2000) and on recent published and unpublished data, including (Francis et al., 2008; Martin et al., 2005) for the HER-2 negative population, (Romond et al., 2005; Slamon et al., 2006) for the HER-2 positive population, (Howell et al., 2005; Thurlimann et al., 2005) for the population receiving adjuvant hormonal therapy, and (Coleman et al., 2014) for the use of adjuvant zoledronic acid in stage II-III breast cancer. Based on the reported event rates, the event rate proportions for disease recurrence in the bone, the viscera, or death reported by (Colleoni et al., 2000) and (Coleman et al., 2014), **and considering the availability of some breast cancer adjuvant therapies,** the **BMFS** rate at three years **is** expected to be approximately **90.5**% in the control group. **Disease recurrence risk after primary breast cancer treatment can vary over time (Cheng et al, 2012). For DFS, assume a piece-wise exponential distribution with a risk of about 5.5% per year for the first 3 years and 3.2% per year afterwards in the control group.**

The primary analysis will be conducted after all enrolled subjects have had the opportunity to complete 5 years of treatment from study day 1. With 4,500 subjects, an enrollment period of approximately **27** months, and a loss to follow-up rate of 6% per year, the study is estimated to reach the primary analysis data cut-off date in approximately **87** months (ie, 7 years and **3** months). **For BMFS, if the true hazard ratio is 0.8, the power to detect superiority of denosumab over placebo in the primary analysis is estimated to be approximately 80%.**

10.4 Access to Individual Subject Treatment Assignments

This is a double-blinded study. Subject treatment assignments will remain blinded to the investigator, study site personnel, subjects, Amgen and Daiichi Sankyo Co., Ltd. study personnel, except as described in Section 5.3, in order to reduce bias. Refer to Section 11.2 for information on when and how the randomization code may be broken.

10.5 Interim Analysis and Early Stopping Guidelines

A DMC external to Amgen and external to Daiichi Sankyo Co., Ltd. will be formed with members consisting of individuals chosen for their expertise in oncology and bone disease. Members of the DMC will include, at a minimum, physicians external to Amgen and Daiichi Sankyo Co., Ltd., and appropriate statistical representation external to

Amgen and Daiichi Sankyo Co., Ltd. The role of this independent DMC will be to monitor safety and efficacy data.

The DMC will review safety data at regular intervals, as outlined in the DMC charter (approximately twice yearly; the start date will depend on subject accrual rates), and will conduct **1** interim **analysis** of efficacy. It is recognized that the DMC may feel ethically compelled to recommend early stopping in the event of overwhelming efficacy. The stopping rules are defined as follows:

1. There **is 1** formal interim **analysis** after approximately 367 subjects have developed bone metastasis or died, and approximately 555 subjects have developed any disease recurrence or died, whichever occurs last. Th**is** interim **analysis** may be performed as soon as approximately 6 months after the sufficient event number has been reached for either BMFS or DFS in the full study population, even if the event number for the other endpoint has not been reached. The critical p-values for rejecting the null or alternative hypothesis are listed in the following table. The multiplicity from testing DFS in the full study population and in the postmenopausal subset simultaneously will be adjusted based on a Hochberg procedure (Sakamaki, 2013; Ye et al., 2012). The study could potentially be stopped if both BMFS and DFS in the full study population cross their corresponding efficacy boundaries, or if BMFS crosses the futility boundary at **the** interim analysis. The other secondary endpoints OS and DRFS will only be tested when the study is stopped or at the **primary** analysis; the same **procedure** as for BMFS will be used to adjust for multiplicity **between the interim and primary analysis** for each of these endpoints.

Table 2. Decision Rule (1-sided) at Interim/Primary Analyses

Analysis	Reject H0	Reject H1
Interim Analysis	BMFS: P <0.0015 DFS in the full study population: P <0.0004 or P<0.0015 for both the full study population and the subset DFS in the subset: P <0.0004 or P<0.0015 for both the full study population and the subset	P >0.9333 for BMFS
Primary Analysis[a]	BMFS: P < 0.02**47** DFS in the full study population: P < 0.01**25**; or P < 0.02**49** for the full study population and **P < 0.0248 for** the subset DFS in the subset: P < 0.01**25**; or P < 0.02**49** for the full study population and **P < 0.0248 for** the subset	

[a] **Boundaries are based on the estimated number of events and will be recalculated based on the actual observed number of events.**

2. At other interim evaluations, the DMC will focus on safety, and will review efficacy data only to balance the risk-benefit assessment. At these analyses, the guideline is that p-values for both BMFS and DFS of less than 0.0005 will be used as evidence of overwhelming efficacy to stop the study.

3. **At the primary analysis that is time-driven, the exact number of events for the primary and secondary endpoints are not fixed and the final alpha boundaries can potentially vary. Table 2 includes the boundaries calculated according to the estimated total numbers of events. In order to strictly control the overall type I error rate, the final boundaries will be updated based on the actual number of events achieved and the alpha levels that have been spent at the interim analysis (Proschan et al, 2006).**

In addition, the DMC will communicate major safety concerns and recommendations regarding study modification or termination to Amgen Inc senior management at any time during the conduct of the study.

Records of all meetings will be archived. Selected Amgen staff may serve as liaisons to the external DMC, but will not be voting members, and will not be unblinded to the results. Details regarding the DMC will be provided in the DMC charter.

10.6 Planned Methods of Analysis

10.6.1 General Approach/Considerations

Amgen will set a primary analysis data cut-off date **after all enrolled subjects have had the opportunity to complete 5 years of treatment from study day 1.** The primary analysis will be based on the data from randomization through the primary analysis data cut-off date.

The primary efficacy endpoint, BMFS, will be analyzed using a log-rank test stratified by the randomization stratification factors. If denosumab is determined to be superior to placebo with respect to the primary efficacy endpoint, the secondary efficacy endpoints including

- Step 1: DFS in the full study population and DFS in the postmenopausal subset
- Step 2: OS
- Step 3: DRFS

will be tested in a stepwise fashion over 3 steps; ie, the treatment effect with respect to the secondary endpoints at the subsequent step will be tested only when denosumab is determined to be superior to placebo with respect to all the secondary endpoints at previous steps. At Step 1, DFS in the full study population and DFS in the postmenopausal subset will be tested simultaneously using a Hochberg procedure to adjust for multiplicity. The secondary endpoints will be analyzed using a similar stratified log-rank test.

Safety will be evaluated by incidence and severity of adverse events, and toxicity grade shifts in laboratory values. The number and percentage of patients who develop neutralizing anti-denosumab antibodies will be tabulated by study visit.

The principal analysis for the primary and secondary efficacy endpoints will employ the FAS approach (refer to Section 10.2.2.1); the per protocol analysis approach will be considered supportive. Safety analyses will be performed using the Safety Analysis Set.

10.6.2 Analysis of Key Study Endpoints

10.6.2.1 Efficacy Analyses

See Appendix E for Definitions and Criteria for Diagnosis of Breast Cancer Recurrence, including local, regional, and distant disease recurrence.

Primary Endpoint

Bone metastasis-free survival will be determined by the time from randomization to the first observation of bone metastasis or death from any cause. Patients last known to be alive, who have not experienced bone metastasis, are censored at their last assessment date, or at the primary analysis data cut-off date, whichever comes first.

For BMFS, Kaplan-Meier estimates (Kaplan & Meier, 1958) will be graphically displayed, and a log-rank test stratified by the randomization stratification factors, will be used. The hazard ratio of denosumab compared with placebo and its corresponding 95% confidence interval will be estimated by use of a Cox proportional hazards model with treatment group as the independent variable stratified by the randomization stratification factors.

Secondary Efficacy Endpoints

Disease-free survival will be determined by the time from randomization to the first observation of disease recurrence or death from any cause. Subjects last known to be alive, who have not experienced recurrence of disease, are censored at their last assessment date, or at the primary analysis data cut-off date, whichever comes first.

Overall survival will be determined by the time from randomization to death from any cause. Subjects last known to be alive are censored at their last contact date, or at the primary analysis data cut-off date, whichever comes first.

Distant recurrence-free survival will be determined by the time from randomization to the first observation of distant disease recurrence or death from any cause. Subjects last known to be alive who have not experienced distant disease recurrence are censored at their last assessment date or at the primary analysis data cut-off date, whichever comes first.

The secondary endpoints will be analyzed using a similar stratified log-rank test and Cox proportional hazards model as used for the primary endpoint.

Exploratory Efficacy Endpoints

Time to first bone metastasis (excluding deaths) will be determined by the time from randomization to the first observation of bone metastasis. Subjects, who have not experienced bone metastasis, are censored at their last assessment date, or at the primary analysis data cut-off date, whichever comes first.

Time to bone metastasis as site of first recurrence (excluding deaths) will be determined by the time from randomization to the first observation of bone metastasis as site of first disease recurrence. Subjects, who have not experienced bone metastasis as site of first recurrence, are censored at the time of extra-osseous disease recurrence, or at their last assessment date, or at the primary analysis data cut-off date, whichever comes first.

Time to disease recurrence will be determined by the time from randomization to the first observation of disease recurrence, excluding deaths. Subjects, who have not experienced recurrence of disease, are censored at their last assessment date, or at the primary analysis data cut-off date, whichever comes first.

Time to distant recurrence will be determined by the time from randomization to the first observation of distant recurrence, excluding deaths. Subjects, who have not experienced distant recurrence, are censored at their last assessment date, or at the primary analysis data cut-off date, whichever comes first.

Time to first on-study fracture (vertebral or non-vertebral fracture) will be determined by the time from randomization to the first on-study fracture (vertebral or non-vertebral fracture) prior to the development of bone metastasis. Subjects, who have not experienced a fracture on study, are censored at the time of development of bone metastasis, at their last contact date, or at the primary analysis data cut-off date, whichever comes first.

Time to first on-study SRE (defined as any fracture [vertebral or non-vertebral], radiation therapy to bone [including the use of radioisotopes], surgery to bone, or spinal cord compression) will be determined by the time from randomization to the first on-study SRE following the development of bone metastasis. Subjects, who have not experienced an SRE on-study, are censored at the time of their last contact date or at the primary analysis data cut-off date, whichever comes first.

Time to first on-study SRE or hypercalcemia will be determined by the time from randomization to the first on-study SRE or the first report of hypercalcemia following the development of bone metastasis. Subjects, who have not experienced an SRE or

hypercalcemia on-study, are censored at the time of their last contact date or at the primary analysis data cut-off date, whichever comes first.

Time to on-study symptomatic bone metastasis will be determined by the time from randomization to the first observation of bone metastasis which is accompanied by symptom at time of detection. Subjects, who have not experienced a symptomatic bone metastasis on-study, are censored at the time of development of asymptomatic bone metastasis (for cause-specific analysis), at the time of their last assessment date or at the primary analysis data cut-off date, whichever comes first.

Breast density will be determined based on standard mammography imaging and summarized descriptively by time point. Description of breast density will include qualitative assessments according to the Breast Imaging Reporting and Data System (BI-RADS) classification of overall breast composition (D'Orsi et al, 2003).

Pathological variables in tumor tissue from neoadjuvant subjects after surgery will be determined based on the investigator assessment and will be summarized and compared between the treatment groups.

Analgesic use will be analyzed based on the analgesic score (refer to Appendix J for the Analgesic Quantification Algorithm [AQA]) from enrollment to the primary analysis data cut-off date.

BPI-SF Pain Scores will be determined per patient self-report (see Appendix H). The analysis of BPI-SF will include change from baseline and responder analyses.

EQ-5D Health Index Scores will be determined per patient self-report (see Appendix I). The EQ-5D health state index and visual analogue scale will be summarized descriptively by visit.

Serum trough levels of denosumab as well as levels and dynamics of bone turnover markers and potential other pharmacodynamic markers will be described. Levels and (if applicable) dynamics of potential other biomarkers will also be described.

For time to first bone metastasis, time to bone metastasis as site of first recurrence, TTR, time to distant recurrence, time to symptomatic bone metastasis and time to first on-study fracture (vertebral or non-vertebral fracture), time to first SRE, and time to first on-study SRE or HCM, Kaplan-Meier estimates or cumulative incidence function (Kalbfleisch and Prentice, 1980) will be graphically displayed and a stratified log-rank test and a Cox proportional hazards model, stratified by the randomization stratification

factors, will be used, as appropriate. A supportive analysis will use a Cox proportional hazards model stratified by the randomization stratification factors to evaluate the covariates that may modify the outcome.

10.6.2.2 Safety Analyses

Safety data will be summarized for all subjects, who received at least 1 dose of investigational product.

Subject Incidence of Treatment-Emergent Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any adverse events will be analyzed as treatment emergent if the indicator of "Did event start before the first dose of investigational product" is checked as "No" on Adverse Events eCRF pages. Based on the adverse event summary instructions, an adverse event that exists prior to the administration of investigational product and gets worse after the first dose of investigational product will be included as a treatment emergent adverse event. The analysis of adverse events will be descriptive. The subject incidence rates of treatment-emergent adverse events reported through the primary analysis data cut-off date during the adverse event reporting period will be tabulated by system organ class and preferred term. Additional summary tables will be provided separately for serious adverse events, NCI CTCAE grade 3, 4, or 5 adverse events, adverse events leading to investigational product discontinuation, and adverse events leading to study withdrawal. Narratives of deaths and serious adverse events will also be provided. All investigational product related adverse events, serious adverse events, NCI CTCAE grade 3, 4 or 5 adverse events, adverse events leading to investigational product discontinuation, and adverse events leading to study withdrawal will be summarized in the same manner as treatment-emergent adverse events.

Changes in Laboratory Values

Laboratory parameters will be summarized over time using descriptive statistics for recorded values and change from baseline and shifts tables, in which the incidence of shift of toxicity grade (NCI CTCAE v3.0) in recorded values from baseline to "worst" on-study value is displayed by treatment arm. Graphical representations of aggregate data may also be presented for parameters of interests.

Anti-denosumab Antibodies

The incidence and percentage of subjects, who develop anti-denosumab antibodies (binding and neutralizing) at any time, will be tabulated for the subset of subjects, who received denosumab treatment.

10.6.2.3 Exploratory Analyses

Biomarker Analyses

Biomarker analyses to assess the pharmacodynamic response (eg, changes from baseline in bone turnover markers) and exploratory PK analyses will be performed. These may include population PK and PK/pharmacodynamic evaluations and/or pharmacodynamic endpoints/clinical outcomes, to characterize the relationship between PK and pharmacodynamic endpoints and clinical outcomes. All statistical analyses of biomarker and pharmacogenetic data will be considered exploratory. Descriptive statistics will be provided as appropriate. If performed, results of population PK or PK/ pharmacodynamic analyses will be reported separately (ie, not in the Clinical Study Report).

10.6.3 Additional Analyses

10.6.3.1 Subject Accountability

The number of subjects screened, enrolled into the study, and the number of subjects, who received study-specific treatment, will be summarized by treatment arm. Reasons for study and treatment discontinuation will also be summarized.

The number and percentage of subjects eligible for each analysis data set will be presented. Additionally, the number and percentage of subjects with important protocol deviations will be presented by deviation type for all enrolled/randomized subjects. A summary will also be produced by treatment arm and in total over all arms. All demographic and baseline characteristics will be summarized by treatment arm.

10.6.3.2 Concomitant Medications

All concomitant medications will be grouped by medication class and by active ingredient within medication class according to the Amgen concomitant medication dictionary. The number and percentage of subjects receiving each medication will be summarized by active ingredient and medication class for each treatment arm.

10.6.3.3 Other Safety Data

Vital signs, weight, physical examination and performance status data will be summarized using appropriate descriptive statistics, by treatment arm and time.

10.6.4 Final Analysis of Data From Long-term Follow-up

Deaths during the long-term survival follow-up, and from randomization through long-term follow-up, will be summarized.

11. INVESTIGATIONAL PRODUCT

11.1 Denosumab (AMG 162)

Denosumab will be presented as a sterile, clear, colorless to slightly yellow, practically free from particles, preservative free liquid in blinded-label, single-use 3.0 mL glass vials containing approximately 1.7 mL of 70 mg denosumab per mL, [redacted] mM acetate and [redacted]% (w/v) sorbitol at pH [redacted]. Placebo will be presented in identical containers and the formulation will be identical to denosumab with the exception of the protein content.

To obtain the box number assignment for a schedule dose, site personnel will call the IVRS. The box number of investigational product is to be recorded on each subject's investigational product administration eCRF.

Investigational Product Details including labeling, storage, preparation, etc. are provided in the Investigational Product Instruction Manual.

11.2 Access to Treatment Assignments

The identity of investigational product assigned to subject numbers or to individual boxes of investigational product will be available for emergency situations through the IVRS. Authorized site staff will be provided with a unique Personal Identification Number (PIN) to access the IVRS to obtain unblinding information. This PIN is unique to the individual and must not be shared. Refer to Sections 10.4 and 11.2 for conditions and requirements for subject unblinding.

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation.

The principal investigator (or equivalent role in Japan) is strongly encouraged to contact the Amgen study manager or (for Japanese sites only) Daiichi Sankyo Co., Ltd. study manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event and must document the unblinding in the subject's eCRF.

Japan only: The detailed procedure for key code opening will be provided as separate procedure manual.

11.3 Compliance in Investigational Product Administration

When investigational product is dispensed for administration to the subject during the study, the investigator or responsible person will determine the concentration of

compliance with the administration of the investigational product. All used and unused vials must be retained for monitor verification. If the site standard operating procedure is elected as the disposal procedure, the standard operating procedure must be provided to the sponsor. The site specific accountability record must contain a minimum of assigned box number, date received, date dispensed and identification number of the subject administered the medication, quantity of vials administered, quantity of vials dispensed, quantity of vials returned/ remaining, balance forward and person recording the information.

12. REGULATORY OBLIGATIONS

12.1 Informed Consent

An initial generic informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template will be communicated by letter from the clinical study manager to the investigator. The written informed consent document should be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study. The investigator is also responsible for asking the subject if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator shall inform the subject's primary care physician of the subject's participation in the clinical study.

All countries (except Japan): The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily an investigator). The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative.

Japan only: The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject or a legally acceptable representative, and by the person who conducted the informed consent discussion. The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

12.2 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form(s), other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form(s) must be received by Amgen or (for Japanese sites only)
Daiichi Sankyo Co., Ltd., before recruitment of subjects into the study and shipment of investigational product.

All countries (except Japan): The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IEC/IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator will be responsible for obtaining annual IEC/IRB approval/ renewal throughout the duration of the study. Copies of the investigator's reports and the IEC/IRB continuance of approval must be sent to Amgen.

Japan only: The head of the medical institution must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The head of the medical institution should notify the IEC/IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Daiichi Sankyo Co., Ltd., in accordance with local procedures.

The investigator will be responsible for obtaining annual approval/renewal of the head of the medical institution throughout the duration of the study. The investigator must retain copies of their reports and the head of the medical institution's continuance of approval.

12.3 Pre-study Documentation Requirements

All countries (except Japan): The investigator is responsible for forwarding the following documents to Amgen for review before study initiation from Amgen or its designee can occur:

Japan only: The medical institution is responsible for forwarding the following documents to Amgen for review before study initiation from Amgen or its designee can occur:

- Signed and dated protocol signature page (Investigator's Agreement)
- Copy of approved informed consent form and subject information sheet, if applicable
- Copy of the IEC/IRB approval of the protocol, consent form, and subject information sheet
- Up-to-date curricula vitae of principal investigator (or equivalent role in Japan) and all co/subinvestigators
- IEC/IRB composition and/or written statement that IEC/IRB is in compliance with regulations
- Signed study contract
- Completed FDA form 1572 (or equivalent)
- Other country-specific forms, as defined in the country-specific requirements
- Completed Financial Disclosure statements for the principal investigator (or equivalent role in Japan), all subinvestigators, and their spouses (legal partners) and dependent children

12.4 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- On the case report forms or other documents submitted to Amgen, or (for Japanese sites only) to Daiichi Sankyo Co., Ltd., subjects should be identified by a subject study number only.
- On Serious Adverse Event forms submitted to Amgen, or (for Japanese sites only) to Daiichi Sankyo Co., Ltd., subjects should be identified by their initials and a subject study number only.
- Documents that are not for submission to Amgen, or (for Japanese sites only) to Daiichi Sankyo Co., Ltd., (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with Federal regulations and ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

Pharmacogenetics Confidentiality (for subjects who sign a separate consent only)
All pharmacogenetics samples and the information associated with the samples will be double-coded and stored in independent, secure databases to ensure confidentiality of the subject's information and to enable destruction of the samples when requested. Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results will not be placed in the subject's medical record and will not be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

12.5 Investigator Signatory Obligations

Each clinical study report should be signed by the coordinating investigator.

The coordinating investigator, identified by Amgen, will either be:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

13. ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 Protocol Amendments and Study Termination

All countries (except Japan): Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of Amgen. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IEC/IRB must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IEC/IRB to Amgen.

Both Amgen and the investigator reserve the right to terminate the study according to the study contract. The investigator should notify the IEC/IRB in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Japan only: Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of Amgen and Daiichi Sankyo Co., Ltd. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The head of the medical institution must be informed of all amendments and give approval. The medical institution must send the approval letter from the head of the medical institution to Daiichi Sankyo Co., Ltd.

Amgen, Daiichi Sankyo Co., Ltd., and the investigator reserve the right to terminate the study, according to the study contract. The investigator should notify the head of the medical institution in writing of the study's completion or early termination, and the head of the medical institution should send the notification to Daiichi Sankyo Co., Ltd.

Subjects may be eligible for continued treatment with investigational product by extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen and (for Japanese sites only) Daiichi Sankyo Co., Ltd. reserve the unilateral right, at their sole discretion, to determine whether to supply the investigational product, and by what mechanism, after termination of the trial and before it is available commercially in this setting.

13.2 Study Documentation and Archive

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on case report forms will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen, Daiichi Sankyo Co., Ltd. (for Japanese sites only), or designee(s), and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed eCRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation (see Section 12.3), and all correspondence to and from the IEC/IRB and Amgen and (for Japanese sites only) Daiichi Sankyo Co., Ltd.

- **All countries (except Japan):** If kept, proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence

- **Japan only:** If kept, delivery sheet, Investigational Product Accountability Record, Return of Investigational Product for Destruction, and all drug-related correspondence.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between Amgen, or (for Japanese sites only) Daiichi Sankyo Co., Ltd., and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify Amgen or (for Japanese sites only) Daiichi Sankyo Co., Ltd., in writing of the new responsible person and/or the new location.

13.3 Study Monitoring and Data Collection

The Amgen, or (for Japanese sites only) Daiichi Sankyo Co., Ltd., representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various

records of the clinical study (eg, [e]CRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen, or (for Japanese sites only) Daiichi Sankyo Co., Ltd., designated monitor is responsible for verifying the case report forms at regular intervals (approximately every 6 weeks) throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the case report forms.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's or (for Japanese sites only) Daiichi Sankyo Co., Ltd.'s Clinical Quality Assurance Department (or designees). Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

All paper case report forms should be typed or filled out with a black ballpoint pen and must be legible.

- Corrections to paper forms will be made by a single line stroke through the error and insertion of the correction above or beside the error. The change must be initialed and dated by the investigator or a member of the study staff authorized by the investigator on the Amgen Delegation of Authority Form. No erasures, correction fluid, or tape may be used.
- Corrections to electronic forms will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review will be performed on subject data received at Amgen, or (for Japanese sites only) Daiichi Sankyo Co., Ltd. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be sent to the site for completion and returned to Amgen, or (for Japanese sites only) Daiichi Sankyo Co., Ltd.
- The principal investigator (or equivalent role in Japan) will sign the Investigator Verification Form to indicate that the principal investigator (or equivalent role in Japan) inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

- Amgen's clinical data management department will correct the database for the following eCRF issues without notification to site staff:
  - misspellings that do not change the meaning of the word (excluding adverse events and medications)
  - location of data recorded on an incorrect eCRF (eg, moving lab data from general comments to the appropriate lab table)
  - date errors that occur into the new year
  - standard time to 24-hour clock
  - temperature unit errors (Fahrenheit vs Centigrade)
  - weight unit errors (pounds vs kilograms) if a baseline weight has been established
  - height unit errors (in. vs cm)
  - administrative data (eg, event names for unscheduled visits or retests)
  - clarifying "other, specify" if data are provided (eg, race, physical exam)
  - correct or enter either "Absolute (A)/Percentage (P)" on hematologies if blank; can be determined from differential data
  - if both the end date and a status of continuing is indicated (eg, for adverse events, concomitant medication, hospitalization), the end date will supersede
  - deletion of obvious duplicate data (eg, same results sent twice with the same date but different clinical planned events—week 4 and early termination)
  - for adverse events that record action taken code = 01 (none) and any other action code, 01 (none) may be deleted as it is superseded by other existing data
  - if equivalent units or terms are recorded instead of the acceptable Amgen/ Daiichi Sankyo Co., Ltd. standard (eg, cc for mL, SQ for SC route, Not Examined for Not Done), the Amgen/ Daiichi Sankyo Co., Ltd. units or terms will be used
  - if the answer to a YES or NO question is blank or obviously incorrect (eg, answers to the following questions do not reflect the data that are recorded or missing: Were there any adverse events? Concomitant medications? Hospitalizations?)
  - correct eCRF page numbers

13.4 Language

Case report forms must be completed in English. TRADENAMES® for concomitant medications may be entered in the local language.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. Consult the country-specific requirements for language requirements.

13.5 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several principal investigators (or equivalent role in

Japan) and appropriate Amgen staff. The committee is expected to solicit input and assistance from other investigators and Amgen staff as appropriate. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship—the criteria described below should be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the **Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals** (International Committee of Medical Journal Editors **2013, updated 2014**), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published**; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.** Authors should meet conditions 1, 2, 3**,** and **4**.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen and (for Japanese sites only) Daiichi Sankyo Co., Ltd. for corporate review. The Clinical Study Agreement among the institution, principal investigator (or equivalent role in Japan), and Amgen will detail the procedures for, and timing of, Amgen's and (for Japanese sites only) Daiichi Sankyo Co., Ltd.'s review of publications.

13.6 Compensation

Subjects will be treated and/or compensated for any study-related illness/injury pursuant to the information provided in the Compensation for Injury section of the Informed Consent.

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15. APPENDICES

Appendix A. Schedule of Assessments

				Treatment Period - Years 1, 2, and 3 (continued on next page)																
Visit	**Screening**			**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**Week 52**	**V10**	**V11**	**V12**	**V13**	**Week 104**	**V14**	**V15**
Week	≤ 24 wks	≤ 4 wks	≤ 2 wks	Q4W (± 7 days)							Q3M (± 14 days)									
Year				1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	3	3
Study Assessments																				
Informed Consent		X																		
Medical / Medication History		X																		
Physical Examination, ECOG Status		X		X			X			X	X	X		X	X	X	X		X	X
Oral Examination		X								X		X			X		X			X
Adverse Event Collection		X		X	X	X	X	X	X	X	X	X		X	X	X	X		X	X
Clinical Fracture / SRE Collection		X		X	X	X	X	X	X	X	X	X		X	X	X	X		X	X
Breast Cancer Therapy Collection		X		X	X	X	X	X	X	X	X	X		X	X	X	X		X	X
Concomitant Medications Collection		X		X	X	X	X	X	X	X	X	X		X	X	X	X		X	X
PRO Questionnaires (BPI-SF, EQ-5D)				X			X			X	X	X		X	X	X	X		X	X
Imaging Assessments																				
Skeletal Scintigraphy	X											------X-----					------X-----			
Mammography, CT/MRI Imaging	X											------X------					------X------			
Investigational Product Administration																				
Denosumab 120 mg or Placebo				X	X	X	X	X	X	X	X	X		X	X	X	X		X	X
Laboratory Assessments																				
Pregnancy Test			X																	
Serum Albumin, Calcium			X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X
Other Serum Values (Mg, P)				X			X			X				X			X			
Hematology (CBC, Differential), Vitamin D				X																
Denosumab Antibody Collection				X						X		X					X			
Denosumab PK Sample Collection *				X			X			X	X	X		X						
Blood Biomarker, BSAP Collection				X			X			X	X	X		X						
Urine Collection				X			X			X	X	X		X						
Tumor Sample Collection		X																		
Follow-up																				
Disease Recurrence/Survival Follow-up																				

Appendix A. Schedule of Assessments

	Treatment Period - Years 3, 4, and 5 (continued)														
Visit	**V16**	**V17**		**V18**	**V19**	**V20**	**V21**	**V22**		**V23**	**V24**	**V25**	**V26**		**EOTP**
Week			**156**	Q3M (± 14 days)					**208**	Q3M (± 14 days)				**260**	265
Year	3	3	3	4	4	4	4	4	4	5	5	5	5	5	6
Study Assessments															
Physical Examination, ECOG Status	X	X		X	X	X	X	X		X	X	X	X		X
Oral Examination		X			X		X			X		X			X
Adverse Event Collection	X	X		X	X	X	X	X		X	X	X	X		X
Clinical Fracture / SRE Collection	X	X		X	X	X	X	X		X	X	X	X		X
Hypercalcemia of Malignancy Collection															X
Breast Cancer Therapy Collection	X	X		X	X	X	X	X		X	X	X	X		X
Concomitant Medications Collection	X	X		X	X	X	X	X		X	X	X	X		X
PRO Questionnaires (BPI-SF, EQ-5D)	X	X		X	X	X	X	X		X	X	X	X		X
Imaging Assessments															
Skeletal Scintigraphy		------X----						------X----					------X------		X
Mammography, CT/MRI Imaging		------X----						------X----					------X------		X
Investigational Product Administration															
Denosumab 120 mg or Placebo	X	X		X	X	X	X	X		X	X	X	X		
Laboratory Assessments															
Serum Albumin, Calcium	X	X		X	X	X	X	X		X	X	X	X		
Other Serum Values (Mg, P)	X				X			X				X			
Vitamin D															X
Denosumab Antibody Collection		X						X					X		X
Denosumab PK Sample Collection *		X													
Blood Biomarker, BSAP Collection		X													
Urine Collection		X													
Tumor Sample Collection															
Follow-up															
Disease Recurrence/Survival Follow-up															

Appendix A. Schedule of Assessments (LTFU)

	Long-term Follow-up				
	Prior to primary analysis data cut-off date			Post-primary analysis data cut-off date	
	All subjects, first 2 visits	All subjects without bone mets	All subjects with documented bone mets		
Visit	**Every 3M**	**Every 3M**	**Every 6M**	**Every 6M**	**Notes**
Year	**6**	**6 to 10**	**6 to 10**	**6 to 10**	
Study Assessments					
Clinical Fracture / SRE Collection	X	X	X		
Hypercalcemia of Malignancy Collection	X	X	X		
Breast Cancer Therapy Collection	X				
Concomitant Medications Collection	X				
PRO Questionnaires (BPI-SF, EQ-5D)	X				
Imaging Assessments					
Skeletal Scintigraphy	Yearly				**See Section 7.2.9**
Mammography, CT/MRI Imaging	Yearly				**See Section 7.2.9**
Laboratory Assessments					
Blood Biomarker, BSAP Collection	**X**	**X**			**As applicable, refer to Section 7.2.10.1**
Tumor Sample Collection	**X**	**X**			**As applicable, refer to Section 7.2.10.3**
Follow-up					
Disease Recurrence	X	X			
Survival	X	X	X	**X**	

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Schedule of Assessments Legend: * at selected sites only; CBC, complete blood cell count; EOTP, End of Treatment Phase Visit; F/U, Follow-up; Mg, magnesium; P, phosphorus; PRO, patient-reported outcomes; Q3M, every 3 months (every 12 weeks ± 14 days); Q4W, every 4 weeks (± 7 days); SRE, skeletal-related event; V, visit; W, week; wks, weeks.

Screening: All screening assessments must be completed and results obtained before randomization into the study. Assessments conducted as standard of care do not require informed consent and may be provided as screening data if conducted within the specified screening windows (see Section 7.1.1). Randomization must occur no more than 8 calendar days before planned study day 1.

Study day 1: The day of first administration of investigational product (denosumab or matching placebo).

Informed Consent must be obtained before any study-specific assessments or procedures are performed.

Medical/ Medication History: The subject's complete medical history will be collected during screening and must date back to at least the original diagnosis of breast cancer, including all applicable treatments for breast cancer, or 5 years, whichever is longer. If a subject is referred to the study center, copies of all applicable reports and histological or cytological evidence confirming the breast cancer diagnosis must be provided to the study center before randomization. Medical history also includes history of other disease processes (active or resolved) and concomitant illnesses.

Physical examination includes vital signs (blood pressure, respiration rate, pulse, and temperature), height (screening only) and weight. For study day 1, a physical exam can be performed up to 3 days before study day 1.

ECOG performance status will be assessed with each physical examination. See Appendix C for assessment of ECOG Performance Status Scale.

Oral Examination: A visual examination of the oral cavity, including teeth, mucosa and jaws will be conducted at baseline and approximately every 6 months thereafter to establish baseline oral health conditions and subsequently to identify any new abnormalities or changes in pre-existing conditions.

Adverse Events: Adverse events must be assessed and documented at each scheduled clinic visit. Subjects must be followed for adverse events for 30 days after the last dose of investigational product, or until all investigational product-related toxicities and ongoing serious adverse events have resolved or are considered stable, whichever is later. Exceptions are hypercalcemia of malignancy, clinical fractures, and SREs, which will be followed **during LTFU prior to primary analysis data cut-off date** (see Sections 7.2.5.1 and 7.2.6).

Clinical Fractures / Skeletal-related Events: Information about any new clinical fractures (prior to the development of bone metastasis) or skeletal-related events (SREs; defined as any pathologic fracture [vertebral or non-vertebral], radiation therapy to bone [including the use of radioisotopes], surgery to bone, or spinal cord compression following the development of bone metastasis) will be assessed and documented at each scheduled clinic visit and during **LTFU prior to primary analysis data cut-off date**. Copies of all screening and on-study radiographic assessments performed to diagnose clinical fractures and SREs must be submitted to the central imaging vendor. Copies of all screening and on-study radiology, surgery, or pathology reports should be kept in the subject's records regardless if corresponding radiographs (or equivalent) are available. See Section 7.2.6 for details. **After primary analysis data cut-off date: Radiographic assessments of events incurred after primary analysis data cut-off date will not be submitted to the central imaging vendor.**

Breast Cancer Therapy: Systemic antineoplastic treatment, radiotherapy, or interventional therapy administered to treat the subject's primary or metastatic breast cancer will be collected.

Concomitant Medications/Treatments: Information regarding type and timing of concomitant medications and treatments will be collected. Calcium and vitamin D supplements will be recorded as concomitant medications.

PRO Questionnaires (BPI-SF and EQ-5D): PRO questionnaires will be completed before any study procedures are performed (including physical exam, laboratory assessments, imaging, and treatment administration). See Section 7.2.8 for details.

Imaging Assessments: All scheduled on-study imaging must be performed within ± 6 weeks of the protocol-specified time point, unless performed within the previous 6 months. All radiological imaging or pathological assessments will be reviewed locally and documented by the investigator on the eCRF. Copies of all screening and on-study imaging assessments performed to monitor or diagnose breast cancer must be submitted to the central imaging vendor. This includes any such images deemed to be negative by the local radiologist and any standard-of-care or routine disease monitoring images performed even if not specified by protocol. Copies of all screening and on-study radiology, surgery, or pathology reports should be kept in the subject's records regardless if corresponding radiographs (or equivalent) are available. **All scheduled imaging will cease after the primary analysis data cut-off date.**

(1) Skeletal Scintigraphy (Full Body Radioisotope Bone Scan): Must be present at screening (performed within 24 weeks of randomization). On-study full body radioisotope bone scans will be performed at the end of year 1 (ie, 52 weeks from study day 1), yearly thereafter (ie, at the end of year 2, 3, etc.), as clinically indicated, to confirm disease recurrence, and at the EOTP visit (unless performed within the past 6 months) (see Appendix A).

Any abnormal bone scan (per central imaging analysis) must be confirmed within 4 weeks of the bone scan using X-ray, CT, MRI or biopsy evidence of lesions consistent with bone metastasis for all areas identified on the bone scan, until documented disease recurrence in the bone (per central imaging analysis or biopsy) (see Section 7.2.9.1).

Assessments for disease recurrence will be performed according to Definitions and Criteria for Diagnosis of Breast Cancer Recurrence outlined in Appendix E. Re-staging will be completed within 4 weeks of either site notification by the central imaging vendor of the subject's first instance of disease recurrence, or histological/cytological confirmation of the subject's first instance of disease recurrence. For the purposes of this protocol, re staging requires the following imaging to be completed: full-body radioisotope bone scan, CT or MRI of the chest, abdomen, and all other suspected sites of disease, and bilateral mammography. In the case of total mastectomy, only mammography of the remaining breast (if applicable) is required. Applicable bone scans, CTs/MRIs, and mammography performed as early as 12 weeks prior to the procedure (imaging, biopsy, or cytology) that confirms disease recurrence will satisfy the restaging requirements, and therefore would not need to be repeated.

(2) Bilateral Mammography and CT or MRI: Bilateral Mammography (except after total mastectomy, in which case only the remaining breast [if applicable] must be imaged) and computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen and all other suspected sites of disease must be present at screening (performed within 24 weeks prior to randomization). On-study and during follow-up, mammography (except after total mastectomy, in which case only the remaining breast [if applicable] must be imaged) and CT or MRI imaging of the chest, abdomen

and all other known or suspected sites of disease will be performed at the end of year 1 (ie, 52 weeks from study day 1), yearly thereafter (ie, at the end of year 2, 3, etc.), as clinically indicated, to confirm disease recurrence, and at the EOTP visit (unless performed within the past 6 months) (see Appendix A). The imaging modality selected should remain the same throughout the study (see Section 7.2.9.1). All scheduled on-study imaging must be performed within ± 6 weeks of the protocol-specified time point, unless performed within the previous 6 months.

Assessments for disease recurrence will be performed according to Definitions and Criteria for Diagnosis of Breast Cancer Recurrence outlined in Appendix E. Re-staging will need to be completed within 4 weeks of either site notification by the central imaging vendor of the subject's first instance of disease recurrence, or histological/cytological confirmation of the subject's first instance of disease recurrence. For the purposes of this protocol, re-staging requires the following imaging to be completed: full-body radioisotope bone scan, CT or MRI of the chest, abdomen, and all other suspected sites of disease, bilateral mammography. In the case of total mastectomy, only mammography of the remaining breast (if applicable) is required. Applicable bone scans, CTs/MRIs, and mammography performed as early as 12 weeks prior to the procedure (imaging, biopsy, or cytology) that confirms disease recurrence will satisfy the restaging requirements, and therefore would not need to be repeated. Extra-osseous disease assessments (mammography and CT or MRI of the chest, abdomen, and all other known or suspected extra-osseous sites of disease) will cease upon documented disease recurrence. All scheduled imaging will cease upon documented disease recurrence in the bone (per central imaging analysis or biopsy).

Pathology Evidence of Disease Recurrence: All pathology assessments (eg, histology or cytology results) will be reviewed locally and documented by the investigator on the eCRF. Copies of all screening and on-study pathology reports should be kept in the subject's records. Assessments for recurrence will be performed according to Definitions and Criteria for Diagnosis of Breast Cancer Recurrence outlined in Appendix E.

Investigational Product Administration: Eligible subjects will receive investigational product (denosumab 120 mg or matching placebo) subcutaneously (SC) every 4 weeks (Q4W) (± 7 days, at least 3 weeks apart) until and including visit 7. This schedule allows subjects receiving standard of care chemotherapies on a Q3W schedule to receive investigational product on a Q3W schedule (+14 days), but no more frequently than every three weeks, to minimize patient clinic visits and enhance adherence to treatment. Following visit 7, investigational product will be administered SC every 3 months (Q3M) (every 12 weeks ± 14 days) for approximately 54 months, for a total duration of approximately 60 months (or until the end of the clinical study, whichever is earlier).

Pregnancy Test: Pregnancy test must be performed for all women of childbearing potential no more than 14 days before randomization. The test must be repeated prior to investigational product administration if the result dates back more than 14 days before randomization. All tests will be performed by the central laboratory.

Laboratory Assessments will include serum albumin, calcium, magnesium (Mg), phosphorus (P), Vitamin D, complete blood cell count (CBC) and differential (see Section 7.2.10). Screening values (or study day 1 pre-dose values, if assessed; see Section 7.2) will be used as baseline values. Note: Laboratory assessments should be performed on the day of the scheduled visit, or within 3 days prior to the visit. If screening samples were collected within 3 days prior to study day 1, then the laboratory assessments performed in screening do not need to be repeated on study day 1.

Urine Collection: Urine must be collected, preferably after the first void in the morning for urine creatinine, urinary N-telopeptide (uNTx) and C-telopeptide (αCTX) analysis.

Anti-denosumab antibodies: Serum for anti-denosumab antibody assay will be collected at baseline (prior to administration of the investigational products on study day 1) **and** on study as outlined in the schedule of assessments.

Blood Biomarkers and **BSAP**: Blood samples for biomarkers and BSAP will be obtained at baseline (prior to administration of investigational products on study day 1), on study as outlined in the Schedule of Assessments, and upon disease recurrence (including both first disease recurrence, and first disease recurrence in the bone, if applicable). See Section 7.3 for details.

Pharmacokinetics (PK): Samples for serum denosumab PK will be obtained on a subset of approximately 120 subjects at selected sites only, at baseline (prior to investigational product administration on study day 1) and on study as outlined in the Schedule of Assessments. See Section 7.2.10 for details.

Tumor Samples: Archived formalin-fixed paraffin-embedded breast tumor samples (surgical specimens or biopsy samples obtained as part of routine care: tumor block or at least 20 charged, unstained slides ascertained to contain tumor cells) along with copies of all corresponding pathology reports will be submitted to the central laboratory at screening and/or as they become available on study. See Section 7.2.10.3 for details.

End of Treatment Phase (EOTP) Visit: will be completed per Schedule of Assessments (± 14 days), or at any time once an individual subject discontinues study participation (4 weeks [+ 7 days] after the last dose of investigational product).

All EOTP assessments must be completed (unless done within the prior 4 weeks), except imaging assessments, which do not need to be repeated if completed within the prior 6 months (ie**,** 24 weeks).

Long-term Follow-up: After completing the treatment phase of the study (60 months from study day 1; or as specified in Section 7.1.2.3 and Section 7.1.3), subjects will be **enter LTFU for approximately 5 years (total study duration for an individual subject is up to 10 years from the date of randomization). The study requirements during LTFU are determined by the primary analysis data cut-off date, refer to Section 7.1.4.1 for assessments prior to primary analysis data cut-off date and Section 7.1.4.2 for assessments required after primary analysis data cut-off date.**

Appendix B. Adverse Event Severity Scoring System

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

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

Appendix C. ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Scale

0 - Fully active, able to carry out all pre-disease performance without restriction.

1 - Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).

2 - Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 - Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.

5 - Dead.

Karnofsky Performance Status

100% - Normal; no complaints; no evidence of disease.

90% - Able to carry on normal activity; minor signs or symptoms of disease.

80% - Normal activity with effort; some signs or symptoms of disease.

70% - Cares for self, unable to carry on normal activity or do active work.

60% - Requires occasional assistance, but is able to care for most personal needs.

50% - Requires considerable assistance and frequent medical care.

40% - Severely disabled; hospitalization indicated, although death not imminent.

30% - Severely disabled; hospitalization necessary; active support treatment is necessary.

20% - Very sick; hospitalization necessary; active support treatment is necessary.

10% - Moribund; fatal processes progressing rapidly.

0% - Dead.

Conversion between Karnofsky and ECOG Performance Status

Karnofsky Score of 100 - 90% corresponds to ECOG 0

Karnofsky Score of 80 - 70% corresponds to ECOG 1

Karnofsky Score of 60 - 50% corresponds to ECOG 2

Karnofsky Score of 40 - 30% corresponds to ECOG 3

Karnofsky Score of 20 - 10% corresponds to ECOG 4

Karnofsky Score of 0% corresponds to ECOG 5

Appendix D. Breast Cancer Grading and Staging

Histopathological Grading of Breast Cancer

(Elston & Ellis, 2002; Fitzgibbons et al., 2000)

Tumor grade will be determined according to the Nottingham Combined Histological Grading System, based on morphological features (tubule formation, nuclear pleomorphism, and mitotic count), by assigning a value of 1 (favorable) to 3 (unfavorable) for each feature. Scores for the 3 categories are then added to give a combined histopathologic grade score.

Total Score	Histopathologic Grade (G)
3, 4, or 5	G1 (low grade; favorable)
6 or 7	G2 (intermediate grade)
8 or 9	G3 (high grade; unfavorable)

TNM Classification and AJCC Stage Groups of Breast Cancer

Information is provided for quick reference only. Please refer to the AJCC Staging Manual 7th edition for details, including "Rules for Classification" for clinical and pathological staging (Edge et al., 2009).

TNM Classification

Primary tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma *in situ*
  - Tis (DCIS): Ductal carcinoma *in situ*
  - Tis (LCIS): Lobular carcinoma *in situ*
  - Tis (Paget): Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and the characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
- T1: Tumor ≤ 20 mm in greatest dimension
  - T1mi: Tumor ≤ 1 mm in greatest dimension
  - T1a: Tumor > 1 mm but ≤ 5 mm in greatest dimension
  - T1b: Tumor > 5 mm but ≤ 10 mm in greatest dimension
  - T1c: Tumor > 10 mm but ≤ 20 mm in greatest dimension

- T2: Tumor > 20 mm but ≤ 50 mm in greatest dimension
- T3: Tumor > 50 mm in greatest dimension
- T4: Tumor of any size with direct extension to chest wall and/or to the skin (ulceration or skin nodules).

  Note: Invasion of the dermis alone does not qualify as T4.
  - T4a: Extension to chest wall, not including only pectoralis muscle adherence/invasion
  - T4b: Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet criteria for inflammatory carcinoma
  - T4c: Both T4a and T4b
  - T4d: Inflammatory carcinoma
    (see "Rules for Classification" [Edge et al., 2009; pp 428ff])

Posttreatment ypT. Clinical (pretreatment) T will be defined by clinical and radiographic findings, while y pathologic (posttreatment) T will be determined by pathologic size and extension. The ypT will be measured as the largest single focus of invasive tumor, with the modifier "m" indicating multiple foci. The measurement of the largest tumor focus should not include areas of fibrosis within the tumor bed. The inclusion of additional information in the pathology report such as distance over which the tumor foci extend, the number of tumor foci present, or the number of slides/ blocks in which tumor appears may assist the clinician in estimating the extent of disease. A comparison of the cellularity in the initial biopsy to that in the posttreatment specimen may also aid in the assessment of response.

Note: If a cancer was designated as inflammatory before neoadjuvant chemotherapy, the patient will be designated to have inflammatory breast cancer throughout, even if the patient has complete response of inflammatory findings.

Regional lymph nodes (N)

Clinical

- NX: Regional lymph nodes cannot be assessed (eg, previously removed)
- N0: No regional lymph node metastases
- N1: Metastases to movable ipsilateral level I, II axillary lymph node(s)
- N2: Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis
  - N2a: Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
  - N2b: Metastases only in clinically detected* ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastases

- N3: Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
    - N3a: Metastases in ipsilateral infraclavicular lymph node(s)
    - N3b: Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
    - N3c: Metastases in ipsilateral supraclavicular lymph node(s)

* *Note: Clinically detected* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel lymph node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

Pathologic (pN)*

- pNX: Regional lymph nodes cannot be assessed (eg, previously removed, or not removed for pathologic study)
- pN0: No regional lymph node metastasis identified histologically

Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

- pN0(i-): No regional lymph node metastases histologically, negative IHC
- pN0(i+): Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
- pN0(mol-): No regional lymph node metastases histologically, negative molecular findings (RT-PCR)

- pN0(mol+): Positive molecular findings (RT-PCR),** but no regional lymph node metastases detected by histology or IHC
- pN1: Micrometastases; or metastases in one to three axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***
    - pN1mi: Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
    - pN1a: Metastases in one to three axillary lymph nodes, at least one metastasis greater than 2.0 mm
    - pN1b: Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
    - pN1c: Metastases in one to three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
- pN2: Metastases in four to nine axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
    - pN2a: Metastases in four to nine axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
    - pN2b: Metastases in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
- pN3: Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***; or in ipsilateral supraclavicular lymph nodes
    - pN3a: Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
    - pN3b: Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
    - pN3c: Metastases in ipsilateral supraclavicular lymph nodes

Notes: * Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for “sentinel node”, for example, pN0(sn).

** RT-PCR: reverse transcriptase-polymerase chain reaction.

*** ”Not clinically detected” is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by by clinical examination.

**** "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

Posttreatment ypN

- Post-treatment yp "N" should be evaluated as for clinical (pretreatment) "N" methods above. The modifier "sn" is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed that the axillary nodal evaluation was by axillary node dissection (AND).
- The X classification will be used (ypNX) if no yp posttreatment SN or AND was performed.
- N categories are the same as those used for pN.

Distant metastases (M)

- M0: No clinical or radiographic evidence of distant metastases
    - cM0(i+): No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
- M1: Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Posttreatment yp M classification. The M category for patients treated with neoadjuvant therapy is the category assigned in the clinical stage, prior to initiation of neoadjuvant therapy. Identification of distant metastases after the start of therapy in cases where pretherapy evaluation showed no metastases is considered progression of disease. If a patient was designated to have detectable distant metastases (M1) before chemotherapy, the patient will be designated as M1 throughout.

AJCC Stage Groupings

AJCC Stage	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Note:
* T1 includes T1mi.
**T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

- M0 includes M0(i+).
- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered stage IV and remains stage IV regardless of response to neoadjuvant therapy.
- Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
- Postneoadjuvant therapy is designated with “yc” or “yp” prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

Appendix E. Definitions and Criteria for Diagnosis of Breast Cancer Recurrence

The criteria for diagnosis of breast cancer recurrence for the purpose of this study are defined below. Treatment of breast cancer recurrence will be at the discretion of the investigator.

Definitions

Local recurrence is defined as the development of breast cancer in any soft tissue or skin of the ipsilateral chest wall after surgical (± radiation) treatment with curative intent.

Regional recurrence is defined as the development of breast cancer in the regional lymph nodes, including ipsilateral axillary, ipsilateral internal mammary, ipsilateral supraclavicular, and/or ipsilateral infraclavicular lymph nodes, and/or in the soft tissue of the ipsilateral axilla, after surgical (± radiation) treatment with curative intent.

Distant recurrence is defined as the development of breast cancer in any distant site (including the skin, subcutaneous tissue [other than skin or subcutaneous tissue areas identified above], and the contralateral breast, within others) and/or distant lymph nodes (ie**,** any lymph nodes other than local or regional lymph nodes as defined above).

Development of non-breast cancer new primary malignancies will not be considered recurrence events.

Diagnostic criteria

Local and regional recurrence of breast cancer must be confirmed by positive biopsy or cytology.

Distant recurrence of breast cancer must be confirmed by positive biopsy, cytology, or by radiological evidence of metastatic disease.

Evidence of disseminated tumor cells in bone marrow is not sufficient for determination of disease recurrence.

Note: If a solitary metastatic lesion is present in only one organ, the diagnosis of breast cancer recurrence must be confirmed using biopsy or cytology, unless medically contra-indicated. Cytology or biopsy is required for diagnosis of malignant effusion (eg, pleural effusion, pericardial effusion, or ascites) or meningeal carcinomatosis (cerebrospinal fluid).

Any positive skeletal scintigraphy (‘bone scan’) (per central imaging analysis) must be confirmed using X-ray, CT, MRI, or biopsy evidence of lesions consistent with bone metastasis.

The date of breast cancer recurrence will be considered as the date of the first abnormal imaging test or clinical observation (in case of superficial lesions only) that is subsequently confirmed.

Methods of Assessment

Wherever possible, the same method of assessment (eg, CT or MRI) and the same technique (eg, spiral CT with contrast) should be used throughout the study. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

Appendix F. Pregnancy Notification Worksheet

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20060359

Study Design: ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____) _____ **Fax** (____) _____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm ___ / dd ___ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
Denosumab				mm ___ /dd ___ /yyyy ____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ___ /dd ___ /yyyy ____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm ___ / dd ___ / yyyy ____ ☐ Unknown

Estimated date of delivery mm ___ / dd ___ / yyyy ____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm ___ / dd ___ / yyyy ____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm ___ / dd ___ / yyyy ____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

A modified Pregnancy Notification Worksheet may be used in Japan, in accordance with local requirements.

Appendix G. Serious Adverse Event Worksheet/Electronic Serious Adverse Event Contingency Report Form

AMGEN Study # 20060359 Denosumab	Electronic Serious Adverse Event (eSAE) Contingency Reporting Form For Restricted Use

Complete either Section A *or* Section B and follow the instructions provided:

Section A

☐ **EDC system (eg, Rave) is active for this study but is not accessible to allow reporting within 24 hours of the Investigator's knowledge of the event. I am submitting (check/complete all that apply):**

☐ An event that applies to a specialty CRF page titled _____ (eg, clinical fracture)

☐ Screening event (as defined by the protocol) **OR** ☐ On-study event (as defined by the protocol)

- *Complete ONLY Sections 1, 2 and 3 (page 1)*
- *Sign and date the signature section following Section 3*
- *Fax completed page of the form to the number noted in the header above Section 1*

Section B

☐ **Access to the EDC system (eg, Rave) has either not begun or has ended for this study. I am submitting (check all that apply):**

☐ Screening event (as defined by the protocol)
- ☐ This is a new event report
- ☐ This is follow-up information for a previously reported event

OR

☐ Event after access to the EDC system (eg, Rave) has ended (*provide subject's End of Study date in Section 2*)
- ☐ This is a new event report
- ☐ This is follow-up information for a previously reported event

- *Complete ALL sections of the form (all 3 pages)*
- *Sign and date the signature section at the end of the form*
- *Fax completed form (all 3 pages) to the number noted in the header above Section 1*

<<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth Day Month Year	Sex ☐F ☐M	Race	If applicable, provide End of Study date

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____ and start date: Day _____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day____ Month____ Year_____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the event may have been caused by IP? No ✓ Yes ✓	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

If you temporarily cannot access the EDC system (eg, Rave), sign below and submit ONLY this page to the number noted in the header above Section 1.

Signature of Investigator or Designee -	Title	Date
_____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the Investigator for this study, or by a Qualified Medical Person authorized by the Investigator for this study.*		

FORM-056006 Version 2.0 Effective Date 07-May-2012

Page 1 of 3

AMGEN Study # 20060359 Denosumab	Electronic Serious Adverse Event (eSAE) Contingency Reporting Form For Restricted Use

If **access to the EDC system (eg, Rave) has either not begun or has ended for this study, *complete the remainder of this form.***

Site Number	Subject ID Number

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes, If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP administered prior to this event? ☐No ☐Yes, If yes, please complete all of Section 5

IMP: _____ ☐ (✓) Blinded ☐ (✓) Open Label	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld

6. RELEVANT CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Relevant Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No ✓	 Yes ✓	Continuing No ✓	 Yes ✓	Dose	Route	Freq.	Treatment Med No ✓	 Yes ✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Date Day Month Year	Test Unit											

AMGEN
Study # 20060359
Denosumab

Electronic Serious Adverse Event (eSAE) Contingency Reporting Form

For Restricted Use

Site Number	Subject ID Number

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee -	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.		

FORM-056006 *Version 2.0 Effective Date 07-May-2012*

Page 3 of 3

A modified Serious Adverse Event Report Form may be used in Japan, in accordance with local requirements.

Appendix H. Brief Pain Inventory – Short Form (BPI-SF)

1903

Date: ☐☐ / ☐☐ / ☐☐
(month) (day) (year)

Subject's Initials : _____

Study Subject #: ☐☐☐☐

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

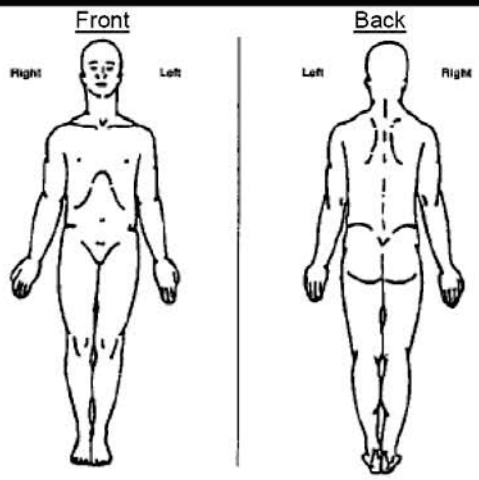
PLEASE USE BLACK INK PEN

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Page 2 of 2

Appendix I. Health Utility Index (EQ-5D)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression

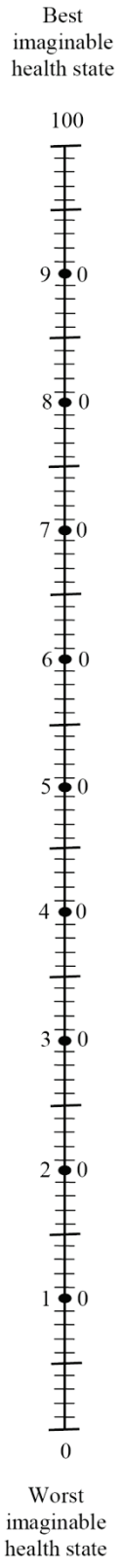
I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

 2

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix J. Analgesic Quantification Algorithm (AQA)

AQA Score	Type of pain medication administered
0	No analgesics
1	Non-opioid analgesics
2	Weak opioids (eg, meperidine, codeine)
3	Strong opioids ≤ 75 mg OME per day
4	Strong opioids 76 - 150 mg OME per day
5	Strong opioids 151 - 300 mg OME per day
6	Strong opioids 301 - 600 mg OME per day
7	Strong opioids > 600 mg OME per day

OME = Oral Morphine Equivalent

Appendix K. Lactation Notification Worksheet

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20060359

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____) _____ **Fax** (____) _____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
Denosumab				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: _____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2. Page 1 of 1

Amendment 4

Protocol Title: 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)

Amgen Protocol Number (Denosumab) 20060359

IND # 9838

EudraCT number 2009-011299-32

Amendment Date: 17 October 2016

Rationale:

The D-CARE study has been ongoing since January 2010. During the course of the study, a considerable gap developed between the expected and observed number of BMFS as well as DFS events (primary and secondary endpoints, respectively). There are several reasons that may explain the divergence of the observed event rate from the expected event rate.

Epidemiologic studies have demonstrated that the recurrence risk in breast cancer is highest during the first 3 to 5 years, with a peak at about 18 months after diagnosis (Cheng et al, 2012; Demicheli et al, 1996). During initial protocol development, a linear event rate was assumed. Furthermore, in recent years, the adoption of more effective therapies, including optimization of aromatase inhibitor therapy for hormone-positive disease and the widespread use of anti-HER2 therapy for HER2 positive breast cancer, may have contributed to lower disease recurrence overall.

Based on the current BMFS event total and BMFS event rate, there will be a substantial delay in the time to reach the BMFS event target for the primary analysis, and there is considerable risk of continued delays. Moreover, based on the DFS event total and event rate, it appears that the DFS event target required for the primary analysis will not be reached at all. The D-CARE steering committee, an advisory group of key investigators participating in the study, recommended that a landmark primary analysis triggered when all enrolled subjects have the opportunity to complete 5 years of treatment on investigational product would be the best approach for the study analysis

given the considerable challenges to achieving event targets. The 5-year mark is also typically used in clinical trials.

Therefore, this protocol is being amended to:

- Change the primary analysis from an event-driven analysis to a landmark (time-based) analysis, triggered when all subjects have the opportunity to complete 5 years treatment with investigational product.
- Remove the second interim analysis from the study to avoid the situation whereby the primary analysis and second interim analysis occur within a short period of time.
- Remove the open-label phase from the study. The open-label period would only apply if during the course of the blinded treatment phase, denosumab was determined to be superior and have a positive benefit/risk profile compared to placebo. The read-out would occur at the interim analyses. Because the second IA was removed, the open-label period is also removed since all subjects will have completed the blinded study treatment prior to the primary analysis.
- Redefine long-term follow-up visit frequency and assessments before and after the primary analysis cut-off date to avoid unnecessary data collection and burden to sites and subjects.
- Update protocol to align with the current protocol template, such as, safety definition and reporting language (as well as pregnancy and lactation reporting forms), and publication policy.

Description of Changes:

Section: Global

Change: Version dates updated throughout document from 18 March 2015 to **17 October 2016**.

Section: Global

Change: Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.

Section: Title Page, Title

Replace: Started withTitle: 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)

With: **Protocol** Title: 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)

Section: Title Page, Key Sponsor Contact

Replace: PPD

Clinical Research Study Manager

Thousand Oaks, CA 91320-1799, USA

PPD

PPD

With: PPD

Global Clinical **Trial** Manager

1 Uxbridge Business Park, Sanderson Road

Uxbridge, UK UB8 1DH

PPD

PPD

Section: Title Page

Add: **Amendment 4 Date:** **17 October 2016**

Section: Investigator's Agreement, For Japanese Sites Only

Replace: Vice President,

Clinical Development Department II

R&D Division, Daiichi Sankyo Co., Ltd.

With: Vice President,

Oncology Clinical Development Department

Daiichi Sankyo Co., Ltd.

Section: Synopsis, Study Design, Paragraph 2

Add: Subjects who develop bone metastasis will permanently discontinue investigational treatment, complete the End of Treatment Phase (EOTP) visit, and enter **long-term** follow-up **(LTFU)** upon documented evidence (per central imaging analysis or biopsy). **For an individual subject, the maximum duration of LTFU after completing the EOTP visit is 5 years (total study duration for an individual subject is up to 10 years from the date of randomization).**

Section: Synopsis, Study Design, Paragraph 3

Delete: ~~After completing the treatment phase of the study, subjects will be followed by clinic visit or telephone contact approximately monthly for 6 months to assess clinical outcomes, approximately every 3 months thereafter to assess SREs, hypercalcemia, disease recurrence status, and survival (until documented evidence of bone metastasis), and approximately every 6 months thereafter to assess SREs, hypercalcemia, and survival, for up to 10 years (120 months) from the date of randomization.~~

Section: Synopsis, Study Design, Paragraphs 4 and 5

Replace: A data monitoring committee (DMC) external to Amgen and external to Daiichi Sankyo Co., Ltd. will review safety data at regular intervals, as outlined in the DMC charter (approximately twice yearly; the start date will depend on subject accrual rates), and will conduct two interim analyses of efficacy; the first after approximately 367 subjects have developed bone metastasis or died, and approximately 555 subjects have developed any disease recurrence or died, whichever comes last; and the second after approximately 551 subjects have developed bone metastasis or died, and approximately 833 subjects have developed any disease recurrence or died, whichever comes last. The respective interim analyses may be conducted early, as soon as approximately 6 months after the sufficient event number has been reached for either BMFS or DFS in the full study population, even if the event number for the other endpoint has not been reached.

The primary analysis will be conducted after approximately 735 subjects have developed bone metastasis or died, and approximately 1110 subjects in the full study population and 512 subjects in the postmenopausal subset have developed any disease recurrence or died, whichever comes last. Subjects will remain on blinded treatment until the primary analysis is completed. If denosumab is determined to be superior and have a positive benefit/risk profile compared with placebo, then all subjects, who remain on blinded study treatment, will be offered open-label denosumab 120 mg SC according to their scheduled study procedures, for a total treatment duration of 5 years from their date of first dose of investigational product (study day 1), or until documented evidence of bone metastasis (per investigator report), or until denosumab is commercially available for the treatment of early-stage breast cancer, whichever comes first. If denosumab is not determined to have a positive benefit/risk profile compared with placebo, then all subjects will complete the EOTP visit and enter follow-up for survival (approximately every 6 months for up to 10 years [120 months] from the date of randomization).

With: A data monitoring committee (DMC) external to Amgen and external to Daiichi Sankyo Co., Ltd. will review safety data at regular intervals, as outlined in the DMC charter (approximately twice yearly; the start date will depend on subject accrual rates), and will conduct **1** interim **analysis** of efficacy after approximately 367 subjects have developed bone metastasis or died, and approximately 555 subjects have developed any disease recurrence or died, whichever comes last. Th**is** interim analys**i**s may be conducted early, as soon as approximately 6 months after the sufficient event number has been reached for either BMFS or DFS in the full study population, even if the event number for the other endpoint has not been reached.

The primary analysis will be conducted after **all enrolled subjects have had the opportunity to complete 5 years of treatment from study day 1.**

Section: Synopsis, Investigational Product Dosage and Administration, Paragraph 4

Delete: ~~Subjects will remain on blinded treatment until the primary analysis is completed. If denosumab is determined to be superior and have a positive benefit/risk profile compared with placebo, then all subjects, who remain on blinded study treatment, will be offered open-label denosumab 120 mg SC according to their scheduled study procedures, for a total treatment duration of 5 years from their first dose of investigational product (study day 1), or until documented evidence of bone metastasis (per investigator report), or until denosumab is commercially available for the treatment of early-stage breast cancer, whichever is earlier. If denosumab is not determined to have a positive benefit/risk profile compared with placebo, then all subjects will complete the EOTP visit and enter follow-up for survival (approximately every 6 months for up to 10 years [120 months] from the date of randomization).~~

Section: Synopsis, Investigational Product Dosage and Administration, Paragraph 4

Add: Administration of investigational products (denosumab or placebo) will be withheld for any subject who experiences a grade 3 or 4 adverse event per Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 reported by the investigator as related to investigational product, **atypical femoral fracture (AFF)** or osteonecrosis of the jaw (ONJ)**,** as determined by the investigator or by an independent expert panel.

Section: Synopsis, Key Study Procedures, Paragraph 4

Replace: Treatment and Follow-up: Subjects will receive investigational product for up to 5 years from study day 1 (treatment period), and will then be followed by clinic visit or telephone contact approximately monthly (Q4W ± 7 days) for six months to assess clinical outcomes (SREs, hypercalcemia of malignancy, concomitant medications, breast cancer therapy, patient-reported outcomes [BPI-SF, EQ-5D], disease recurrence status [until documented evidence of bone metastasis], and survival), approximately every 3 months (every 12 weeks ± 14 days) thereafter to assess SREs, hypercalcemia, disease recurrence status, and survival (until documented evidence of bone metastasis), and approximately every 6 months (± 1 month) thereafter to assess SREs, hypercalcemia, and survival, for up to 10 years (120 months) from the date of randomization.

With: Treatment and Follow-up: Subjects will receive investigational product for up to 5 years from study day 1 (treatment period), and will **then enter LTFU for approximately 5 years (60 months) following the EOTP visit. The expected total study duration for an individual subject is up to 10 years from the randomization date.**

Section: Synopsis, Key Study Procedures, Paragraph 7

Delete: ~~*Blinded Treatment Phase:*~~ The following assessments will be performed at various visits (see Appendix A):

Section: Synopsis, Key Study Procedures, Paragraph 8

Delete: ~~*Open-Label Treatment Phase:* The following assessments will be performed at various visits (see Appendix A): ECOG performance status; physical examination including vital signs (temperature, pulse, blood pressure, respiratory rate) and weight; oral examination; clinical fractures and SREs; breast cancer therapy; concomitant medications; hematology; serum chemistry; denosumab PK (subjects participating in the PK substudy who received blinded denosumab on study); anti-denosumab antibodies. Adverse events and concomitant medications will be recorded throughout the study.~~

Section: Synopsis, Statistical Considerations, Paragraph 1

Replace: The key secondary objective is to compare the treatment effect of denosumab with that of placebo on prolonging DFS in the full study population or in the postmenopausal subset.

With: The key secondary objective is to compare the treatment effect of denosumab with that of placebo on prolonging DFS in the full study population **and** in the postmenopausal subset.

Section: Synopsis, Statistical Considerations, Paragraphs 2 to 3

Replace: Key efficacy analyses: Two interim analyses of efficacy will be conducted; the first after approximately 367 subjects have developed bone metastasis or died, and approximately 555 subjects in the full study population have developed any disease recurrence or died, whichever comes last; and the second after approximately 551 subjects have developed bone metastasis or died, and approximately 833 subjects in the full study population have developed any disease recurrence or died, whichever comes last. The respective interim analyses may be conducted early, as soon as approximately 6 months after the sufficient event number has been reached for either BMFS or DFS in the full study population, even if the event number for the other endpoint has not been reached.

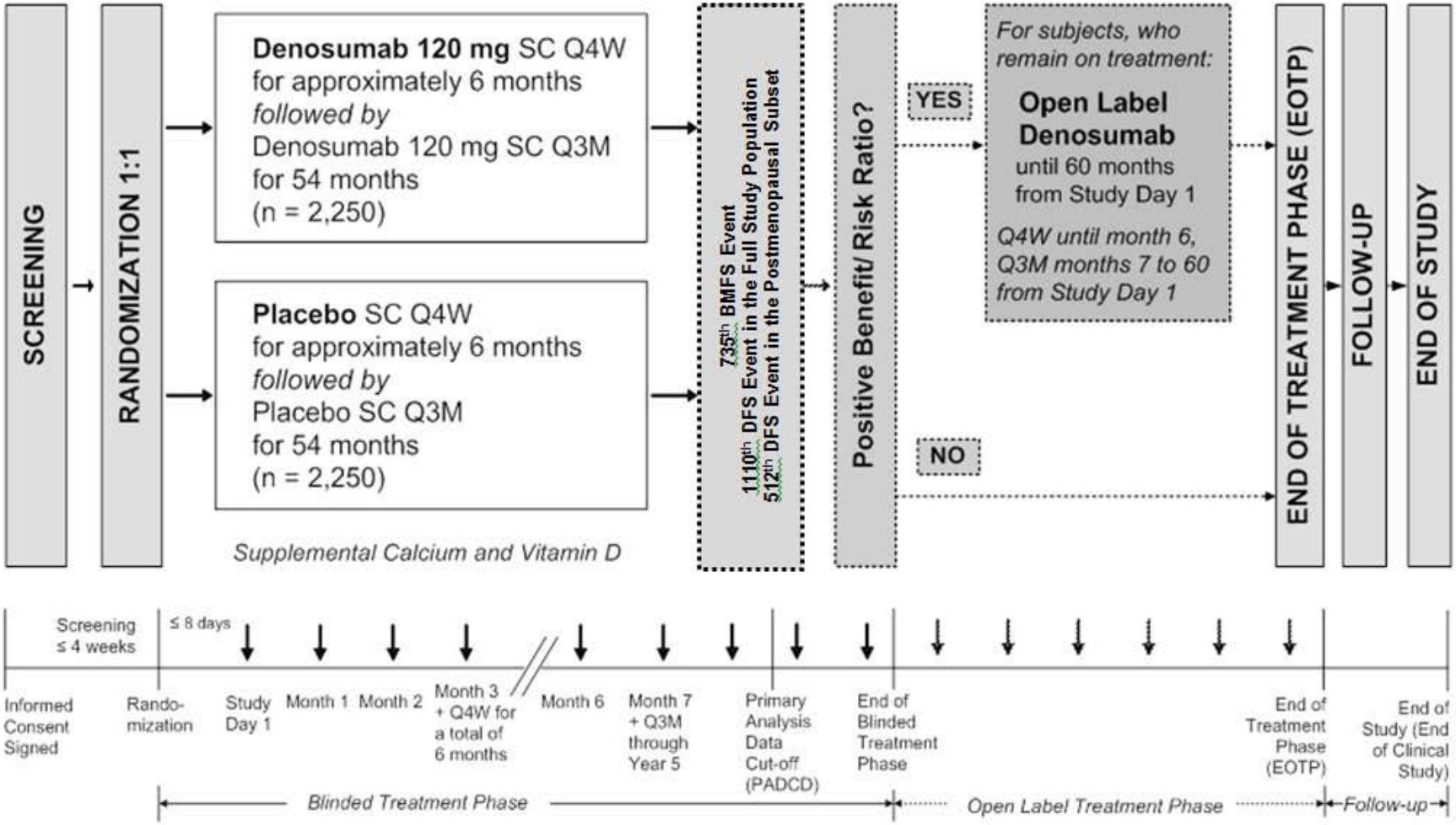
The primary analysis will be performed after approximately 735 subjects have developed bone metastasis or died, and approximately 1110 subjects in the full study population and approximately 512 subjects in the postmenopausal subset have developed any disease recurrence or died, whichever comes last.

With: Key efficacy analyses: **One** interim analys**i**s of efficacy will be conducted; after approximately 367 subjects have developed bone metastasis or died, and approximately 555 subjects in the full study population have developed any disease recurrence or died, whichever comes last. Th**is** interim analys**i**s may be conducted early, as soon as approximately 6 months after the sufficient event number has been reached for either BMFS or DFS in the full study population, even if the event number for the other endpoint has not been reached.

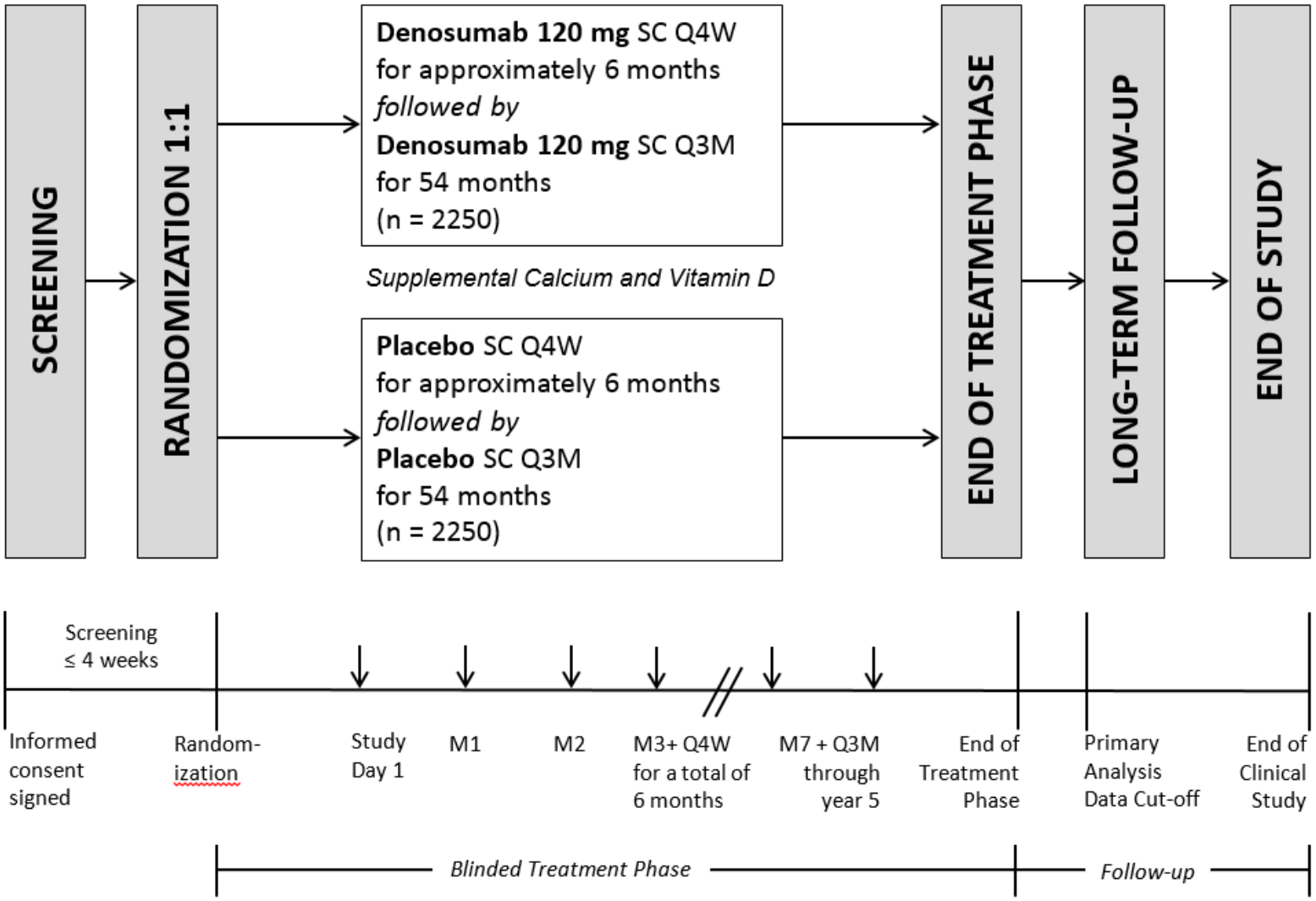
The primary analysis will be **conducted after all enrolled subjects have had the opportunity to complete 5 years of treatment from study day 1.**

Section: Study Schema

Replace:



With:


SCREENING
RANDOMIZATION 1:1
Denosumab 120 mg SC Q4W
for approximately 6 months
followed by
Denosumab 120 mg SC Q3M
for 54 months
(n = 2250)
Supplemental Calcium and Vitamin D
Placebo SC Q4W
for approximately 6 months
followed by
Placebo SC Q3M
for 54 months
(n = 2250)
END OF TREATMENT PHASE
LONG-TERM FOLLOW-UP
END OF STUDY
Screening
≤ 4 weeks
Informed consent signed
Random-ization
Study Day 1
M1
M2
M3+ Q4W for a total of 6 months
M7 + Q3M through year 5
End of Treatment Phase
Primary Analysis Data Cut-off
End of Clinical Study
Blinded Treatment Phase
Follow-up

Section: Study Glossary

Add:

EU	**European Union**
LTFU	**Long-term follow-up**

Section: Study Glossary

Replace:

Primary Analysis Data Cut-off Date (primary completion)	Amgen will set a primary analysis data cut-off date in anticipation of approximately 735 subjects having developed bone metastasis or died, and approximately 1110 subjects in the full study population and 512 subjects in the postmenopausal subset having developed any disease recurrence or died, whichever comes last. The primary analysis will be based on the data from randomization through the primary analysis data cut-off date.

With:

Primary Analysis Data Cut-off Date (primary completion)	Amgen will set a primary analysis data cut-off date in anticipation of **all enrolled subjects having had the opportunity to complete 5 years of treatment from study day 1**. The primary analysis will be based on the data from randomization through the primary analysis data cut-off date.

Section: Study Glossary

Delete:

~~End of Blinded Treatment Phase~~ ~~(for the clinical study)~~	~~If denosumab is determined to be superior and have a positive benefit/risk profile compared with placebo, then the end of the blinded treatment phase is defined as approximately 12 weeks after the last dose of investigation product in the blinded treatment phase.~~ ~~If the benefit/risk profile is not positive, then the end of the blinded treatment phase is defined as approximately 4 weeks after the last dose of denosumab in the blinded treatment phase.~~
~~Open-Label Treatment Phase~~	~~If denosumab is determined to be superior and have a positive benefit/risk profile compared with placebo, then all subjects, who remain on blinded study treatment, will be offered open-label denosumab 120 mg SC according to their scheduled study procedures, for a total treatment duration of 5 years (approximately 60 months) from their study day 1, or until documented evidence of bone metastasis (per investigator report), or until denosumab is commercially available for the treatment of early-stage breast cancer, whichever comes first.~~

Section: Study Glossary

Delete:

End of Treatment Phase (EOTP) (for an individual participant)	An individual subject may receive investigational product for up to 5 years (ie**,** 60 months) from the day of first dose of investigational product (study day 1), or until documented evidence of bone metastasis (per central imaging analysis or biopsy), ~~or (for subjects on open-label denosumab only) until documented evidence of bone metastasis (per investigator report), or until denosumab is commercially available for the treatment of early-stage breast cancer,~~ whichever is earlier. See Section 3.4.1.

Section: 2.6. Hypotheses, Paragraph 2

Replace: It is anticipated that the true HR of denosumab compared with placebo is 0.83 in the full study population or in the postmenopausal subset.

With: It is anticipated that the true HR of denosumab compared with placebo is 0.83 in the full study population **and 0.76** in the postmenopausal subset.

Section: 3.1. Study Design, Paragraph 1

Delete: Approximately 4,500 subjects will be randomized in a 1:1 ratio to receive denosumab 120 mg or matching placebo SC Q4W (± 7 days) for approximately 6 months followed by denosumab 120 mg or matching placebo SC every Q3M (ie**,** every 12 weeks ± 14 days) for 4½ years (approximately 54 months), for a total treatment duration of 5 years (approximately 60 months)~~, or until the end of the blinded treatment phase, whichever is earlier~~.

Section: 3.1. Study Design, Paragraphs 3 to 4

Replace: A data monitoring committee (DMC) external to Amgen and external to Daiichi Sankyo Co., Ltd. will review safety data at regular intervals, as outlined in the DMC charter (approximately twice yearly; the start date will depend on subject accrual rates). This external DMC will conduct two interim analyses of efficacy; the first after approximately 367 subjects have developed bone metastasis or died, and approximately 555 subjects have developed any disease recurrence or died, whichever comes last; and the second after approximately 551 subjects have developed bone metastasis or died, and approximately 833 subjects have developed any disease recurrence or died, whichever comes last. To ensure timely conduct of the

respective interim analyses, the interim analyses may be conducted early, as soon as approximately 6 months after the sufficient event number has been reached for either BMFS or DFS in the full study population, even if the event number for the other endpoint has not been reached.

The primary analysis will be conducted after approximately 735 subjects have developed bone metastasis or died, and approximately 1110 subjects in the full study population and 512 subjects in the postmenopausal subset have developed any disease recurrence or died, whichever comes last. Subjects will remain on blinded treatment until the primary analysis is completed. If denosumab is determined to be superior and have a positive benefit/risk profile compared with placebo, then all subjects, who remain on blinded study treatment, will be offered open-label denosumab 120 mg SC according to their scheduled study procedures, for a total treatment duration of 5 years from their day of first dose of investigational product (study day 1), or until documented evidence of bone metastasis (per investigator report), or until denosumab is commercially available for the treatment of early-stage breast cancer, whichever comes first. If denosumab is not determined to have a positive benefit/risk profile compared with placebo, then all subjects will complete the EOTP visit and enter follow-up for survival (approximately every 6 months for up to 10 years [120 months] from the date of randomization).

With: A data monitoring committee (DMC) external to Amgen and external to Daiichi Sankyo Co., Ltd. will review safety data at regular intervals, as outlined in the DMC charter (approximately twice yearly; the start date will depend on subject accrual rates). This external DMC will conduct **1** interim **analysis** of efficacy after approximately 367 subjects have developed bone metastasis or died, and approximately 555 subjects have developed any disease recurrence or died, whichever comes last**.** To ensure timely conduct of the interim **analysis**, the interim **analysis** may be conducted early, as soon as approximately 6 months after the sufficient event number has been reached for either BMFS or DFS in the full study population, even if the event number for the other endpoint has not been reached.

The primary analysis will be conducted after **all enrolled subjects have had the opportunity to complete 5 years of treatment from study day 1.**

Section: 3.3. Number of Subjects, Paragraph 1

Delete: Participants in this clinical investigation shall be referred to as "subjects". Approximately 2,250 subjects will be randomized to each treatment group, for a total planned sample size of approximately 4,500 subjects. ~~Amgen may choose to increase sample size to ensure timely completion of the study, e.g. if the event rate is lower than expected.~~ Refer to Section 10.3 for details on the rationale for the number of subjects.

Section: 3.4.1. Study Duration for Individual Participants, Paragraph 1

Delete: An individual subject may receive investigational product treatment for up to 5 years (ie**,** 60 months) from the day of first dose of investigational product (study day 1), or until documented evidence of bone metastasis (per central imaging analysis or biopsy),~~ or (for subjects on open-label denosumab only) until documented evidence of bone metastasis (per investigator report), or until denosumab is commercially available for the treatment of early-stage breast cancer,~~ whichever is earlier (treatment phase).

Section: 3.4.1. Study Duration for Individual Participants, Paragraph 2

Replace: After completing the treatment phase of the study, subjects will be followed by clinic visit or telephone contact approximately monthly (Q4W ± 7 days) for six months to assess clinical outcomes. After the first six months, subjects will be followed approximately every 3 months (every 12 weeks ± 14 days) thereafter to assess SREs, hypercalcemia, disease recurrence status, and survival. If there is documented evidence of bone metastasis, the frequency of follow-up visits will change to approximately every 6 months (± 1 month) to assess SREs, hypercalcemia, and survival for up to 10 years (120 months) from the date of randomization.

With: After completing the treatment phase of the study, subjects will be followed by clinic visit or telephone contact for up to **5** years (**60** months) from the **EOTP visit (total study duration for an individual subject is up to 10 years from the date of randomization)**. **Follow-up procedures are detailed in Section 7.1.4.**

Section: 3.4.2. Duration of the Clinical Study, Paragraph 1

Replace: The anticipated duration of the blinded treatment phase is approximately 93 months (ie 7 years and 9 months) from first subject enrolled. This represents time to recruit approximately 4,500 subjects (approximately 30 months) and time for approximately 735 subjects to experience bone metastasis or death, and for approximately 1110 subjects in the full study population and 512 subjects in the postmenopausal subset to experience any disease recurrence or death, whichever comes last, as well as continued blinded treatment until the primary analysis is complete and the benefit/risk profile of denosumab is determined. Actual study duration may vary depending on observed event rates.

With: The anticipated duration **from first subject enrolled to the primary completion of the study** is approximately **87** months (ie**,** 7 years and **3** months). This represents time to recruit approximately 4,500 subjects (approximately **27** months) and time for **all subjects to have the opportunity to complete 5 years of blinded treatment**.

Section: 3.4.2. Duration of the Clinical Study, Paragraph 2

Delete: ~~Amgen will monitor the overall event rate pooled by treatment group, and will set a data cut-off date for the primary analysis in anticipation of approximately 735 subjects having experienced bone metastasis or death, and approximately 1110 subjects in the full study population and 512 subjects in the postmenopausal subset having experienced disease recurrence or death. Amgen may choose to increase the sample size in order to ensure timely completion of the study.~~

Section: 3.4.2. Duration of the Clinical Study, Paragraph 2

Replace: The anticipated overall duration of the clinical study, including the recruitment period (approximately 2.5 years [30 months]), the treatment period (approximately 5 years [60 months], and the follow-up period (approximately 5 years [60 months]), will be approximately 12.5 years or approximately 150 months.

With: The anticipated overall duration of the clinical study, including the recruitment period (approximately 2.5 years [**27** months]), the treatment period (approximately 5 years [60 months]**)**, and the follow-up period (approximately 5 years [60 months]), will be approximately 12.5 years or approximately 150 months.

Section: 3.4.3. End of Study (End of the Clinical Study), Paragraph 1

Replace: Amgen will set a primary analysis data cut-off date in anticipation of approximately 735 subjects having developed bone metastasis or died, and approximately 1110 subjects in the full study population and 512 subjects in the postmenopausal subset having developed any disease recurrence or died, whichever comes last. The primary analysis will be based on the data from randomization through the primary analysis data cut-off date and is considered the primary completion of the study.

With: **The primary analysis will be conducted after all enrolled subjects have had the opportunity to complete 5 years of treatment from study day 1.** The primary analysis will be based on the data from randomization through the primary analysis data cut-off date and is considered the primary completion of the study.

Section: 3.4.3. End of Study (End of the Clinical Study), Paragraph 2

Replace: The End of Study (End of the Clinical Study) is defined as the date that the last subject is assessed in the follow-up phase. With 30 months of enrollment and the last subject anticipated to be on study for 10 years (ie., 120 months), the end of study is anticipated to be approximately 12.5 years (ie., approximately 150 months) from the first subject enrolled.

With: The End of Study (End of the Clinical Study) is defined as the date that the last subject is assessed in the follow-up phase. With **27** months of enrollment and the last subject anticipated to be on study for **up to** 10 years (ie, 120 months), the end of study is anticipated to be approximately 12.5 years (ie, approximately 150 months) from the first subject enrolled.

Section: 6.1. Investigational Product Dosage, Administration, and Schedule, Paragraph 3

Delete: The total treatment duration will be 5 years (approximately 60 months) ~~or until the end of the blinded treatment phase, whichever is earlier~~.

Section: 6.5. Dose Escalation and Dose Stopping Rules, Paragraph 2

Add: Administration of investigational product (denosumab or placebo) will be withheld for any subject who experiences a grade 3 or 4 adverse event per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 reported by the investigator as related to investigational product, **atypical femoral fracture (AFF),** or osteonecrosis of the jaw (ONJ)**,** as determined by the investigator or by an independent expert panel.

Section: 7.1.2.1. Study Treatment, Paragraph 1

Delete: ~~Blinded Treatment Phase~~

Study treatment (investigational product: denosumab at a dose of 120 mg or matching placebo) will be administered by a licensed healthcare professional SC Q4W (±7 days, at least 3 weeks apart; see Section 6.1) for approximately 6 months, followed by investigational product SC Q3M (ie**,** every 12 weeks ± 14 days) for 4½ years (approximately 54 months), for a total treatment duration of 5 years (approximately 60 months), or until documented evidence of bone metastasis (per central imaging analysis or biopsy), ~~or until the end of the blinded treatment phase,~~ whichever is earlier. During the first approximate 6 months of treatment, investigational product may be administered Q3W to subjects receiving or scheduled to receive Q3W adjuvant/neoadjuvant chemotherapy (see Section 6.1). There must be at least a 3-week interval between administrations of investigational product.

~~Open-Label Treatment Phase~~

~~Subjects will remain on blinded treatment until the primary analysis is completed. If denosumab is determined to be superior and have a positive benefit/risk profile compared with placebo, then all subjects, who remain on blinded study treatment, will be offered open-label denosumab 120 mg SC according to their scheduled study procedures, for a total treatment duration~~

~~of 5 years from their date of first dose of investigational product (study day 1), or until documented evidence of bone metastasis (per investigator report), or until denosumab is commercially available for the treatment of early-stage breast cancer, whichever is earlier.~~

Section: 7.1.3. End of Treatment Phase (EOTP), Paragraphs 2 to 4

Delete: ~~If denosumab is not determined to have a positive benefit/risk profile compared with placebo, then all subjects will complete the EOTP visit 4 weeks (+ 7 days) after their last dose of investigational product.~~

All EOTP assessments must be completed (unless done within the prior 4 weeks), except imaging assessments, which do not need to be repeated if completed within the prior 6 months (ie, 24 weeks).

~~If denosumab is not determined to have a positive benefit/risk profile compared with placebo, then no imaging will be required at the EOTP visit.~~

Section: 7.1.4. Follow-up Procedures, entire section

Replace: Blinded Treatment Phase

After completing the treatment phase of the study, subjects will be followed by clinic visit or telephone contact approximately monthly (Q4W ± 7 days) for six months to assess clinical outcomes (SREs, hypercalcemia of malignancy, concomitant medications, breast cancer therapy, patient-reported outcomes [BPI-SF, EQ-5D], disease recurrence status [until documented evidence of bone metastasis {per central imaging analysis or biopsy}] and survival) and approximately every 3 months (every 12 weeks ± 14 days) thereafter to assess SREs, hypercalcemia, disease recurrence status, and survival (until documented evidence of bone metastasis [per central imaging analysis or biopsy]), and approximately every 6 months (± 1 month) thereafter to assess SREs, hypercalcemia, and, survival, for up to 10 years (120 months) from the date of randomization.

Imaging assessments will continue during follow-up per the schedule of assessments (Appendix A), until documented evidence of disease recurrence in the bone (per central imaging analysis or biopsy). See Section 7.2.9 for details.

One serum sample to evaluate for the presence of anti-denosumab antibodies will be collected approximately 6 months (24 weeks ± 14 days) after the last investigational product administration. In addition, biomarker samples will be taken at the time of disease recurrence (including both first disease recurrence, and first disease recurrence in the bone, if applicable).

Open-Label Treatment Phase

After completing the open-label treatment phase of the study, subjects will be followed by clinic visit or telephone contact approximately every 3 months (every 12 weeks ± 14 days) to assess disease recurrence status and survival (until documented evidence of bone metastasis [per investigator report]), and approximately every 6 months (± 1 month) thereafter to assess survival, for up to 10 years (120 months) from the date of randomization.

There will be no scheduled imaging assessments during the open-label treatment phase.

One serum sample to evaluate for the presence of anti-denosumab antibodies will be collected approximately 6 months (24 weeks ± 14 days) after the last investigational product administration. In addition, biomarker samples will be taken at the time of disease recurrence (including both first disease recurrence, and first disease recurrence in the bone, if applicable).

Follow-up if Benefit/Risk Profile is Not Determined to be Positive

If denosumab is <u>not</u> determined to have a positive benefit/risk profile compared with placebo, then all subjects will complete the EOTP visit and enter follow-up for survival (approximately every 6 months for up to 10 years [120 months] from the date of randomization).

One serum sample to evaluate for the presence of anti-denosumab antibodies will be collected approximately 6 months (24 weeks ± 14 days) after the last investigational product administration.

There will be no scheduled imaging assessments, and no other scheduled procedures.

With: After completing the treatment phase of the study, subjects will **then enter LTFU for approximately 5 years (60 months) following the EOTP visit. The study requirements during LTFU are different before and after primary analysis data cut-off date and are detailed in Section 7.1.4.1 (before primary analysis data cut-off date) and Section 7.1.4.2 (after primary analysis data cut-off date).**

7.1.4.1. LTFU Requirements Prior to the Primary Analysis Data Cut-off Date

All subjects (including subjects with documented evidence of bone metastasis) should be followed by clinic visit or telephone contact every 3 months (every 12 weeks ± 14 days) for approximately 6 months (ie, first 2 visits of LTFU following EOTP).

- **The following assessments are required:**
  - **clinical fractures/SREs**
  - **hypercalcemia of malignancy**
  - **breast cancer therapy**
  - **concomitant medications**
  - **patient-reported outcomes (BPI-SF, EQ-5D)**
  - **disease recurrence status (until documented evidence of bone metastasis [per central imaging analysis or biopsy]). Not required for subjects with documented evidence of bone metastasis**
  - **survival**

All subjects <u>without</u> documented evidence of bone metastasis:

following the completion of the initial 6 month LTFU period, subjects should be followed by clinic visit or telephone contact every 3 months (every 12 weeks ± 14 days).

- **The following assessments are required:**
  - **clinical fractures/SREs**
  - **hypercalcemia**
  - **disease recurrence status (until documented evidence of bone metastasis [per central imaging analysis or biopsy])**
  - **survival**

Imaging assessments will continue during **LTFU** per the schedule of assessments (Appendix A), until documented evidence of disease recurrence

in the bone (per central imaging analysis or biopsy). See Section 7.2.9 for details.

Biomarker samples will be taken at the time of disease recurrence (including both first disease recurrence, and first disease recurrence in the bone, if applicable).

Subjects <u>with</u> documented evidence of bone metastasis including subjects whose bone metastasis is confirmed after the initial 6 month (per central imaging analysis or biopsy): following the completion of the initial 6 month LTFU period, subjects should be followed by clinic visit or telephone contact every 6 months (± 1 month).

- **The following assessments are required:**
  - **SREs**
  - **hypercalcemia**
  - **survival**

7.1.4.2. LTFU Requirements After the Primary Analysis Data Cut-off Date

Following the primary analysis data cut-off date, all subjects should complete the EOTP visit and will be followed by clinic visit or telephone contact every 6 months (± 1 month) for survival only. All scheduled imaging and all other assessments (except survival) will cease after the primary analysis data cut-off date.

Section: 7.2.5. Adverse Event Collection

Replace: Exceptions are hypercalcemia of malignancy, clinical fractures, and SREs, which will be followed until the End of Study (see Sections 7.2.5.1 and 7.2.6).

With: Exceptions are hypercalcemia of malignancy, clinical fractures, and SREs, which will **continue to** be **collected during LTFU prior to primary analysis data cut-off date** (see Sections 7.2.5.1 and 7.2.6).

Section: 7.2.5.1. Hypercalcemia of Malignancy

Replace: Clinical events of hypercalcemia of malignancy will be collected on the eCRF throughout the study and during the follow-up.

With: Clinical events of hypercalcemia of malignancy will be collected on the eCRF throughout the study and during **LTFU prior to primary analysis data cut-off date**.

Section: 7.2.6. Clinical Fracture and Skeletal-related Event Collection, Paragraphs 6 to 7

Replace: Information about any new clinical fractures or SREs will be assessed and documented on the eCRF at each scheduled clinic visit and during the follow-up. Copies of all radiographic assessments performed to diagnose clinical fractures and SREs must be submitted to the central imaging vendor. Copies of all screening and on-study radiology, surgery, or pathology reports should be kept in the subject's records regardless if corresponding radiographs (or equivalent) are available.

Open-Label Treatment Phase: Radiographic assessments of events incurred during the open-label treatment phase will not be submitted to the central imaging vendor.

With: Information about any new clinical fractures **(prior to the development of bone metastasis)** or SREs will be assessed and documented on the eCRF at each scheduled clinic visit and during **LTFU prior to primary analysis data cut-off date**. Copies of all radiographic assessments performed to diagnose clinical fractures and SREs must be submitted to the central imaging vendor. Copies of all screening and on-study radiology, surgery, or pathology reports should be kept in the subject's records regardless if corresponding radiographs (or equivalent) are available.

Radiographic assessments for clinical fractures and SREs collected after primary analysis data cut-off date will not be submitted to the central imaging vendor.

Section: 7.2.8. Patient Reported Outcomes, Paragraph 2

Delete: ~~Open-Label Treatment Phase: There will be no collection of patient reported outcomes during the open-label treatment phase.~~

Section: 7.2.9.1. Disease Assessments (Mammography, Bone Scan, CT/MRI), Paragraph 2

Add: All scheduled on-study imaging must be performed within ± 6 weeks of the protocol-specified time point, unless performed within the previous 6 months. **All scheduled imaging will cease after the primary analysis data cut-off date.**

Section: 7.2.9.1. Disease Assessments (Mammography, Bone Scan, CT/MRI), Paragraph 3

Delete: ~~Open-Label Treatment Phase: There will be no protocol required imaging assessments during the open-label treatment phase.~~

Section: 7.2.10.1. Blood Assessments, Paragraphs 4-8

Delete: ~~Open-Label Treatment Phase: After subjects have been unblinded, there will be no scheduled collection of PK samples for subjects, who switch from placebo to open-label denosumab. Subjects, who switch from blinded denosumab to open-label denosumab will continue PK sampling per the schedule of assessments.~~

The centers that will participate in this part of the study will be determined at the time of site selection, on the basis of center interest, site ability to obtain and process serum denosumab concentration samples, and recruitment capacity. A competitive enrollment strategy will be used. Serum levels for denosumab will be obtained in randomized subjects at these centers until approximately 120 subjects have been enrolled into the PK portion of the trial (optional for subjects).

Anti-denosumab antibodies: Serum for anti-denosumab antibody assay will be collected at baseline (prior to administration of the investigational products on study day 1)~~,~~ **and** on study as outlined in the schedule of assessments (Appendix A)~~, and one sample during follow-up (approximately 6 months [24 weeks ± 14 days] after the last investigational product administration)~~.

Blood biomarkers and Bone Specific Alkaline Phosphatase (BSAP): Blood for biomarker assessments and BSAP will be obtained at baseline (prior to administration of the investigational products on study day 1), on study as outlined in the schedule of assessments (Appendix A), and upon disease recurrence (including both first disease recurrence, and first disease recurrence in the bone, if applicable).

~~Open-Label Treatment Phase: There will be no scheduled biomarker assessments during the open-label treatment phase.~~

Section: 7.2.10.2. Urine Assessments, Paragraph 4

Delete: ~~Open-Label Treatment Phase: There will be no scheduled urine assessments during the open-label treatment phase.~~

Section: 7.2.10.3. Tumor Samples, Paragraph 2

Delete: ~~Open-Label Treatment Phase: There will be no scheduled tumor sample collection during the open-label treatment phase.~~

Section: 7.3.1. Biomarker Development, Paragraph 3

Delete: ~~Open-Label Treatment Phase: There will be no scheduled biomarker assessments during the open-label treatment phase.~~

Section: 9.1.1. Adverse Events, Paragraphs 2 to 7

Replace: This definition of adverse events is broadened in this study to include any such occurrence (e.g., sign, symptom, or diagnosis) or worsening of a pre-existing medical condition from the time that a subject has signed informed consent to the time of randomization to or initiation of investigational product. Worsening indicates that the pre-existing medical condition (e.g., diabetes, migraine headaches, gout) has increased in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

If infections occur, microbiological investigations (e.g. cultures) should be performed as clinically feasible to identify a causative organism, and specific data should be reported.

Recurrence of breast cancer should not be reported as an adverse event. However, any specific symptoms or sequelae of the disease recurrence (e.g.,

organ failure, respiratory distress, etc) will be considered adverse events and will be captured on the eCRF.

Interventions for pretreatment conditions (e.g., elective surgery) or medical procedures that were planned before study enrollment are not considered adverse events.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events.

With: **The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.**

This definition of adverse events is broadened in this study to include any such occurrence (eg, sign, symptom, or diagnosis) or worsening of a pre-existing medical condition from the time that a subject has signed informed consent to the time of randomization to or initiation of investigational product. Worsening indicates that the pre-existing medical condition **or underlying disease** (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, **and/**or duration **more than would be expected, and/or has** an association with **a** significantly worse outcome **than expected**.

If infections occur, microbiological investigations (eg**,** cultures) should be performed as clinically feasible to identify a causative organism, and specific data should be reported.

Recurrence of breast cancer should not be reported as an adverse event. However, any specific symptoms or sequelae of the disease recurrence (eg, organ failure, respiratory distress, etc) will be considered adverse events and will be captured on the eCRF.

Interventions for pretreatment conditions (eg, elective surgery) or, medical procedures that were planned before study enrollment, are not considered adverse events.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a **clinically significant** change from **the subject's baseline** values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events. **Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event. The investigator is expected to follow reported adverse events until stabilization or reversibility.**

Section: 9.1.2. Serious Adverse Events, Paragraph 1

Add: A serious adverse event is defined as an adverse event that **meets at least 1 of the following criteria:**

Section: 9.1.2. Serious Adverse Events, Paragraph 3

Add: Examples include allergic bronchospasm, convulsions, and blood dyscrasias**, drug-induced liver injury, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention**.

Section: 9.2. Safety Event Reporting Procedures, Section Title

Replace: Reporting Procedures for All Adverse Events

With: **Safety Event** Reporting Procedures

Section: 9.2. Safety Event Reporting Procedures

Add: **9.2.1 Adverse Events**

Section: 9.2.2. Reporting Procedures for Serious Adverse Events, Paragraphs 1 to 4

Replace: 9.3 Serious Adverse Event Reporting Procedures

Serious adverse events will be collected and recorded at least throughout the study period, beginning with the signing of the informed consent until the EOTP, or for 30 days after the last dose of investigational product for subjects who discontinue investigational product before the EOTP. All serious adverse events occurring after the above mentioned criteria will be collected and recorded.

All serious adverse events that occur after the subject has signed the informed consent form must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable electronic Serious Adverse Event (eSAE) eCRF. If the electronic data capture (EDC) system is unavailable to the site staff to report the Serious Adverse Event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the Investigator's knowledge of the event. See Appendix G for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The Investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable eCRF (eg, Adverse Event Summary eCRF).

With: 9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the EOTP, or for 30 days after the last dose of investigational product for subjects who discontinue investigational product before the EOTP**, are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Adverse Event CRF.**

All serious adverse events that occur after the subject has signed the informed consent form must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable electronic Serious Adverse Event (eSAE) eCRF. If the electronic data capture (EDC) system is unavailable to the site staff to report the Serious Adverse Event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the Investigator's knowledge of the event. See Appendix G for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form. **For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSAE Contingency Report Form, the data must be entered into the EDC system when the system is available again.**

The investigator must assess whether the serious adverse event is possibly related to the investigational product and/or other protocol-required therapies. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product? Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new

information. **If specifically requested, t**he Investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable eCRF (eg, Adverse Event Summary eCRF).

Section: 9.2.3. Reporting Serious Adverse Events After the Protocol-required Reporting Period, (new section)

Add: **9.2.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period**

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of following the protocol-required reporting or after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

Section: 9.3. Pregnancy and Lactation Reporting, Paragraphs 2 to 5

Replace: In addition to reporting any pregnancies occurring during the study, Investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 5 months after the end of treatment.

The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program (PSP) within 7 business days of the site receiving notification of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix F). The Pregnancy Surveillance Program will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

With: In addition to reporting any pregnancies occurring during the study, **i**nvestigators should **report** pregnancies that occur **through 5 months** after the last dose of protocol-required therapies.

The pregnancy should be reported to Amgen **G**lobal **Patient Safety** within **24 hours** of the **investigator's knowledge of the event** of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix F). **Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.**

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

Section: 9.3. Pregnancy and Lactation Reporting, Paragraph 8

Replace: Any lactation case should be reported to Amgen's global Lactation Surveillance Program (LSP) within 7 business days of the site receiving notification.

With: Any lactation case should be reported to Amgen **G**lobal **Patient Safety** within **24 hours** of the **investigator's knowledge of event**.

Section: 10.1. Study Design, Paragraphs 2 to 3

Replace: A DMC external to Amgen and external to Daiichi Sankyo Co., Ltd. will review safety data at regular intervals, as outlined in the DMC charter (approximately twice yearly; the start date will depend on subject accrual rates). This external DMC will conduct two interim analyses of efficacy; the first after approximately 367 subjects have developed bone metastasis or died, and approximately 555 subjects have developed any disease recurrence or died, whichever comes last; and the second after approximately 551 subjects have developed bone metastasis or died, and approximately 833 subjects have developed any disease recurrence or died, whichever comes last. To ensure

timely conduct of the respective interim analyses, the interim analyses may be conducted early, as soon as approximately 6 months after the sufficient event number has been reached for either BMFS or DFS in the full study population, even if the event number for the other endpoint has not been reached.

The primary analysis will be conducted after approximately 735 subjects have developed bone metastasis or died, and approximately 1110 subjects in the full study population and 512 subjects in the postmenopausal subset have developed any disease recurrence or died, whichever comes last. Subjects will remain on blinded treatment until the primary analysis is completed.

With: **An external DMC will monitor the study and conduct 1 interim analysis of efficacy. Refer to Section 10.5 for details.**

The primary analysis will be conducted after all enrolled subjects have had the opportunity to complete 5 years of treatment from study day 1.

Section: 10.3 Sample Size Considerations, entire section

Replace: The sample size calculation is based on the primary endpoint, BMFS, and is estimated using EAST 5.2. Estimates of the event rates for BMFS and DFS for the target population are based on (Colleoni et al., 2000) and on recent published and unpublished data, including (Francis et al., 2008; Martin et al., 2005) for the HER-2 negative population, (Romond et al., 2005; Slamon et al., 2006) for the HER-2 positive population, (Howell et al., 2005; Thurlimann et al., 2005) for the population receiving adjuvant hormonal therapy, and (Coleman et al., 2014) for the use of adjuvant zoledronic acid in stage II-III breast cancer. Based on the reported event rates, and based on the event rate proportions for disease recurrence in the bone, the viscera, or death reported by (Colleoni et al., 2000) and (Coleman et al., 2014), the respective rates at three years of BMFS and DFS are expected to be approximately 89% and 83% in the control group.

For BMFS, if the true hazard ratio is 0.8, 735 subjects with an event of bone metastasis or death among the 4,500 planned subjects, of whom about 47% were postmenopausal at enrollment, will provide 85% power to detect superiority of denosumab over placebo. For DFS, assuming a true hazard ratio of 0.83, 1110 subjects in the full study population with an event of

disease recurrence or death, including approximately 512 subjects in the postmenopausal subset, will provide about 80% power to detect superiority of denosumab over placebo. For DFS in the postmenopausal subset, assuming a true hazard ratio of 0.76, approximately 512 postmenopausal subjects with an event of disease recurrence or death will provide about 80% power to detect superiority of denosumab over placebo.

The study will conclude when approximately 735 subjects have developed bone metastasis or died, and approximately 1110 subjects in the full study population and 512 subjects in the postmenopausal subset have developed any disease recurrence or died, whichever comes last. With 4,500 subjects, an enrollment period of approximately 30 months, and a loss to follow-up rate of 6% per year, the study is estimated to reach the primary analysis data cut-off date in approximately 89 months (ie, 7 years and 5 months). The rate of bone metastasis or death and the rate of disease recurrence or death of the pooled treatment groups will be monitored. If the rates are lower than expected, then the sample size may be modified, or the study duration prolonged.

With: The sample size calculation is based on the primary endpoint, BMFS, and is estimated using EAST **6.4**. Estimates of the event rates for BMFS and DFS for the target population are based on (Colleoni et al., 2000) and on recent published and unpublished data, including (Francis et al., 2008; Martin et al., 2005) for the HER-2 negative population, (Romond et al., 2005; Slamon et al., 2006) for the HER-2 positive population, (Howell et al., 2005; Thurlimann et al., 2005) for the population receiving adjuvant hormonal therapy, and (Coleman et al., 2014) for the use of adjuvant zoledronic acid in stage II-III breast cancer. Based on the reported event rates, the event rate proportions for disease recurrence in the bone, the viscera, or death reported by (Colleoni et al., 2000) and (Coleman et al., 2014), **and considering the availability of some breast cancer adjuvant therapies,** the **BMFS** rate at three years **is** expected to be approximately **90.5**% in the control group. **Disease recurrence risk after primary breast cancer treatment can vary over time (Cheng et al, 2012). For DFS, assume a piece-wise exponential distribution with a risk of about 5.5% per year for the first 3 years and 3.2% per year afterwards in the control group.**

The primary analysis will be conducted after all enrolled subjects have had the opportunity to complete 5 years of treatment from study day 1. With 4,500 subjects, an enrollment period of approximately **27** months, and a loss to follow-up rate of 6% per year, the study is estimated to reach the primary analysis data cut-off date in approximately **87** months (ie, 7 years and **3** months). **For BMFS, if the true hazard ratio is 0.8, the power to detect superiority of denosumab over placebo in the primary analysis is estimated to be approximately 80%.**

Section: 10.5. Interim Analysis and Early Stopping Guidelines, Paragraph 2

Replace: The DMC will review safety data at regular intervals, as outlined in the DMC charter (approximately twice yearly; the start date will depend on subject accrual rates), and will conduct two interim analyses of efficacy.

With: The DMC will review safety data at regular intervals, as outlined in the DMC charter (approximately twice yearly; the start date will depend on subject accrual rates), and will conduct **1** interim **analysis** of efficacy.

Section: 10.5. Interim Analysis and Early Stopping Guidelines, Paragraph 2, Bullet 1

Replace: There are two formal interim analyses; the first after approximately 367 subjects have developed bone metastasis or died, and approximately 555 subjects have developed any disease recurrence or died, whichever occurs last; and the second after approximately 551 subjects have developed bone metastasis or died, and approximately 833 subjects have developed any disease recurrence or died, whichever occurs last. The respective interim analyses may be performed as soon as approximately 6 months after the sufficient event number has been reached for either BMFS or DFS in the full study population, even if the event number for the other endpoint has not been reached. The critical p-values for rejecting the null or alternative hypothesis, as determined by the Lan-DeMets spending function with an O'Brien-Fleming approach for efficacy, and the Gamma Family with parameter -14 for futility (BMFS only), are listed in the following table. The multiplicity from testing DFS in the full study population and in the postmenopausal subset simultaneously will be adjusted based on a Hochberg procedure (Sakamaki, 2013; Ye et al., 2012). The study could potentially be stopped if both BMFS and DFS in the full study population

cross their corresponding efficacy boundaries, or if BMFS crosses the futility boundary at either interim analysis. The other secondary endpoints OS and DRFS will only be tested when the study is stopped or at the final analysis; the same Lan-DeMats spending function with an O'Brien-Fleming approach as for BMFS will be used to adjust for multiplicity for each of these endpoints.

With: There **is 1** formal interim **analysis** after approximately 367 subjects have developed bone metastasis or died, and approximately 555 subjects have developed any disease recurrence or died, whichever occurs last. Th**is** interim **analysis** may be performed as soon as approximately 6 months after the sufficient event number has been reached for either BMFS or DFS in the full study population, even if the event number for the other endpoint has not been reached. The critical p-values for rejecting the null or alternative hypothesis are listed in the following table. The multiplicity from testing DFS in the full study population and in the postmenopausal subset simultaneously will be adjusted based on a Hochberg procedure (Sakamaki, 2013; Ye et al., 2012). The study could potentially be stopped if both BMFS and DFS in the full study population cross their corresponding efficacy boundaries, or if BMFS crosses the futility boundary at **the** interim analysis. The other secondary endpoints OS and DRFS will only be tested when the study is stopped or at the **primary** analysis; the same **procedure** as for BMFS will be used to adjust for multiplicity **between the interim and primary analysis** for each of these endpoints.

Section: 10.5. Interim Analysis and Early Stopping Guidelines, Table 2

Replace: Decision rule (1-sided) at interim/ final analyses

Analysis	Reject H0	Reject H1
Interim Analysis 1	BMFS: P <0.0015 DFS in the full study population: P <0.0004 or P<0.0015 for both the full study population and the subset DFS in the subset: P <0.0004 or P<0.0015 for both the full study population and the subset	P >0.9333 for BMFS
Interim Analysis 2	BMFS: P < 0.0092 DFS in the full study population: P < 0.0038; or P < 0.0092 for both the full study population and the subset; or P < 0.0092 if DFS in the subset was rejected at IA #1 DFS in the subset: P < 0.0038; or P < 0.0092 for both the full study population and the subset; or P < 0.0092 if DFS in the full study population was rejected at IA #1	P > 0.4969 for BMFS
Final Analysis	BMFS: P < 0.022 DFS in the full study population: P < 0.0113; or P < 0.022 for both the full study population and the subset or P < 0.022 if DFS in the subset was rejected at any IA DFS in the subset: P < 0.0113; or P < 0.022 for both the full study population and the subset; or P < 0.022 if DFS in the full study population was rejected at any IA	

With:

Table 2. Decision Rule (1-sided) at Interim/Primary Analyses

Analysis	Reject H0	Reject H1
Interim Analysis	BMFS: P <0.0015 DFS in the full study population: P <0.0004 or P<0.0015 for both the full study population and the subset DFS in the subset: P <0.0004 or P<0.0015 for both the full study population and the subset	P >0.9333 for BMFS
Primary Analysis[a]	BMFS: P < 0.02**47** DFS in the full study population: P < 0.01**25**; or P < 0.02**49** for the full study population and **P < 0.0248 for** the subset DFS in the subset: P < 0.01**25**; or P < 0.02**49** for the full study population and **P < 0.0248 for** the subset	

[a] **Boundaries are based on the estimated number of events and will be recalculated based on the actual observed number of events.**

Section: 10.5. Interim Analysis and Early Stopping Guidelines, Paragraph 2, Bullet 3

Add: **3. At the primary analysis that is time-driven, the exact number of events for the primary and secondary endpoints are not fixed and the final alpha boundaries can potentially vary. Table 2 includes the boundaries calculated according to the estimated total numbers of events. In order to strictly control the overall type I error rate, the final boundaries will be updated based on the actual number of events achieved and the alpha levels that have been spent at the interim analysis (Proschan et al, 2006).**

Section: 10.6.1. General Approach/Considerations, Paragraph 1

Replace: Amgen will set a primary analysis data cut-off date in anticipation of approximately 735 subjects having developed bone metastasis or died, and approximately 1110 subjects in the full study population and 512 subjects in the postmenopausal subset having developed any disease recurrence or died, whichever comes last. The primary analysis will be based on the data from randomization through the primary analysis data cut-off date.

With: Amgen will set a primary analysis data cut-off date **after all enrolled subjects have had the opportunity to complete 5 years of treatment from study day 1.** The primary analysis will be based on the data from randomization through the primary analysis data cut-off date.

Section: 10.6.4. Planned Methods of Analysis Through the End of the Blinded Treatment Phase (entire section deleted)

Delete: ~~10.6.4 Planned Methods of Analysis Through the End of the Blinded Treatment Phase~~

~~If appropriate, analyses described in Section 10.6 will be performed based on the data from randomization through end of the blinded treatment phase. These analyses will be supportive and exploratory in nature~~

Section: 10.6.4. Final Analysis of Data From Long-term Follow-up (entire section)

Replace: 10.6.5 Analysis of Data From Follow-up

Selected safety data (including adverse events, laboratory assessments) and efficacy data (including disease recurrence, sites of recurrence, and death) will be summarized for the open-label treatment phase. Events of disease recurrence, sites of recurrence, and deaths during the long-term survival follow-up, and from randomization through long-term follow-up, will also be summarized.

With: 10.6.**4** **Final** Analysis of Data From **Long-term** Follow-up

Deaths during the long-term survival follow-up, and from randomization through long-term follow-up, will be summarized.

Section: 13.5. Publication Policy, Paragraph 2 and Bullet 1

Replace: Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2005), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published**.** Authors should meet conditions 1, 2, and 3.

With: Authorship of any publications resulting from this study will be determined on the basis of the **Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals** (International Committee of Medical Journal Editors **2013, updated 2014**), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published**; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.** Authors should meet conditions 1, 2, 3**,** and **4**.

Section: 14. References

Add: **Cheng L, Swartz MD, Zhao H, et al. Hazard of recurrence among women after primary breast cancer treatment - a 10-year follow-up using data from SEER medicare. *Cancer Epidemiol Biomarkers Prev*. 2012;21(5):800-809.**

Section: 14. References

Add: **Proschan MA, Lan KKG, Wittes JT. Statistical Monitoring of Clinical Trials: A Unified Approach. Springer, New York; 2006.**

Section: Appendix A. Schedule of Assessments

Replace:

	Treatment Period - Years 3, 4, and 5 (continued)														Follow-up		
Visit	**V16**	**V17**		**V18**	**V19**	**V20**	**V21**	**V22**		**V23**	**V24**	**V25**	**V26**		**EOTP**	**6M F/U**	**F/U**
Week			**156**	Q3M (± 14 days)					**208**	Q3M (± 14 days)				**260**	265	266-290	291+
Year	3	3	3	4	4	4	4	4	4	5	5	5	5	5	6	6	6 to 10
Study Assessments																	
Physical Examination, ECOG Status	X	X		X	X	X	X	X		X	X	X	X		X		
Oral Examination		X			X		X			X		X			X		
Adverse Event Collection	X	X		X	X	X	X	X		X	X	X	X		X		
Clinical Fracture / SRE Collection	X	X		X	X	X	X	X		X	X	X	X		X	X	X
Hypercalcemia of Malignancy Collection															X	X	X
Breast Cancer Therapy Collection	X	X		X	X	X	X	X		X	X	X	X		X	X	
Concomitant Medications Collection	X	X		X	X	X	X	X		X	X	X	X		X	X	
PRO Questionnaires (BPI-SF, EQ-5D)	X	X		X	X	X	X	X		X	X	X	X		X	X	
Imaging Assessments																	
Skeletal Scintigraphy		------X------						------X------					-----X------X				X
Mammography, CT/MRI Imaging		------X------						------X------					-----X------X				X
Investigational Product Administration																	
Denosumab 120 mg or Placebo	X	X		X	X	X	X	X		X	X	X	X				
Laboratory Assessments																	
Serum Albumin, Calcium	X	X		X	X	X	X	X		X	X	X	X				
Other Serum Values (Mg, P)	X				X			X				X					
Vitamin D															X		
Denosumab Antibody Collection		X						X					X		X	X	
Denosumab PK Sample Collection *		X															
Blood Biomarker, BSAP Collection		X															
Urine Collection		X															
Tumor Sample Collection																	
Follow-up																	
Disease Recurrence/ Survival Follow-up																X	X

With:

	Treatment Period - Years 3, 4, and 5 (continued)														
Visit	**V16**	**V17**		**V18**	**V19**	**V20**	**V21**	**V22**		**V23**	**V24**	**V25**	**V26**		**EOTP**
Week			**156**	Q3M (± 14 days)					**208**	Q3M (± 14 days)				**260**	265
Year	3	3	3	4	4	4	4	4	4	5	5	5	5	5	6
Study Assessments															
Physical Examination, ECOG Status	X	X		X	X	X	X	X		X	X	X	X		X
Oral Examination		X			X		X			X		X			X
Adverse Event Collection	X	X		X	X	X	X	X		X	X	X	X		X
Clinical Fracture / SRE Collection	X	X		X	X	X	X	X		X	X	X	X		X
Hypercalcemia of Malignancy Collection															X
Breast Cancer Therapy Collection	X	X		X	X	X	X	X		X	X	X	X		X
Concomitant Medications Collection	X	X		X	X	X	X	X		X	X	X	X		X
PRO Questionnaires (BPI-SF, EQ-5D)	X	X		X	X	X	X	X		X	X	X	X		X
Imaging Assessments															
Skeletal Scintigraphy		------X----						------X----					------X------	X	
Mammography, CT/MRI Imaging		------X----						------X----					------X------	X	
Investigational Product Administration															
Denosumab 120 mg or Placebo	X	X		X	X	X	X	X		X	X	X	X		
Laboratory Assessments															
Serum Albumin, Calcium	X	X		X	X	X	X	X		X	X	X	X		
Other Serum Values (Mg, P)	X				X			X				X			
Vitamin D															X
Denosumab Antibody Collection		X						X					X		X
Denosumab PK Sample Collection *		X													
Blood Biomarker, BSAP Collection		X													
Urine Collection		X													
Tumor Sample Collection															
Follow-up															
Disease Recurrence/Survival Follow-up															

	Long-term Follow-up				
	Prior to primary analysis data cut-off date			Post-primary analysis data cut-off date	
Visit	**All subjects, first 2 visits** Every 3M	**All subjects without bone mets** Every 3M	**All subjects with documented bone mets** Every 6M	Every 6M	**Notes**
Year	6	6 to 10	6 to 10	6 to 10	
Study Assessments					
Clinical Fracture / SRE Collection	X	X	X		
Hypercalcemia of Malignancy Collection	X	X	X		
Breast Cancer Therapy Collection	X				
Concomitant Medications Collection	X				
PRO Questionnaires (BPI-SF, EQ-5D)	X				
Imaging Assessments					
Skeletal Scintigraphy	Yearly				**See Section 7.2.9**
Mammography, CT/MRI Imaging	Yearly				**See Section 7.2.9**
Laboratory Assessments					
Blood Biomarker, BSAP Collection	**X**	**X**			**As applicable, refer to Section 7.2.10.1**
Tumor Sample Collection	**X**	**X**			**As applicable, refer to Section 7.2.10.3**
Follow-up					
Disease Recurrence	X	X			
Survival	X	X	X	**X**	

Section: Appendix A. Schedule of Assessments

Delete: ~~**OL1. Open-Label Treatment Phase Schedule of Assessments – Years 1, 2, and 3**~~

~~**Visit**~~	~~**V1**~~	~~**V2**~~	~~**V3**~~	~~**V4**~~	~~**V5**~~	~~**V6**~~	~~**V7**~~	~~**V8**~~	~~**V9**~~	~~**V10**~~	~~**V11**~~	~~**V12**~~	~~**V13**~~
~~Week~~	~~Q4W (+7 days)~~												
~~Year~~	~~1~~	~~1~~	~~1~~	~~1~~	~~1~~	~~1~~	~~1~~	~~1~~	~~1~~	~~2~~	~~2~~	~~2~~	~~2~~
~~**Study Assessments**~~													
~~Physical Examination, ECOG Status~~	~~X~~			~~X~~			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
~~Oral Examination~~							~~X~~		~~X~~		~~X~~		~~X~~
~~Adverse Event Collection~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
~~Clinical Fracture / SRE Collection~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
~~Hypercalcemia of Malignancy Collection~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
~~Breast Cancer Therapy Collection~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
~~Concomitant Medications Collection~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
~~**Investigational Product Administration**~~													
~~Denosumab 120 mg~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
~~**Laboratory Assessments**~~													
~~Serum Albumin, Calcium~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
~~Other Serum Values (Mg, **P**)~~	~~X~~			~~X~~			~~X~~			~~X~~			~~X~~
~~Hematology (CBC, Differential), Vitamin D~~	~~X~~												
~~Denosumab Antibody Collection~~	~~X~~						~~X~~		~~X~~				~~X~~
~~Denosumab PK Sample Collection •~~	~~X~~			~~X~~			~~X~~	~~X~~	~~X~~	~~X~~			
~~**Follow-up**~~													
~~Disease Recurrence/ Survival Follow-up~~													

OL1. Open-Label Treatment Phase Schedule of Assessments – Years 3, 4, and 5

	Open Label Treatment Phase- Years 3, 4, and 5 (continued)											*Follow-up*	
Visit	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**EOTP**	**F/U**
Week			Q3M (+ 14 days)					Q3M (+ 14 days)				265	291 +
Year	3	3	4	4	4	4	4	5	5	5	5	6	6 to 10
Study Assessments													
Physical Examination, ECOG Status	X	X	X	X	X	X	X	X	X	X	X	X	
Oral Examination		X		X		X		X		X		X	
Adverse Event Collection	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Fracture / SRE Collection	X	X	X	X	X	X	X	X	X	X	X	X	
Hypercalcemia of Malignancy Collection	X	X	X	X	X	X	X	X	X	X	X	X	
Breast Cancer Therapy Collection	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications Collection	X	X	X	X	X	X	X	X	X	X	X	X	
Investigational Product Administration													
Denosumab 120 mg	X	X	X	X	X	X	X	X	X	X	X		
Laboratory Assessments													
Serum Albumin, Calcium	X	X	X	X	X	X	X	X	X	X	X		
Other Serum Values (Mg, **P**)	X			X			X			X			
Hematology (CBC, Differential), Vitamin D												X	
Denosumab Antibody Collection		X					X				X	X	
Denosumab PK Sample Collection •		X											
Follow-up													
Disease Recurrence/ Survival Follow-up													X

Section: Appendix A. Schedule of Assessments, Legend

Delete: * at selected sites only; ~~6M F/U, first six months of follow-up period;~~ CBC, complete blood cell count; EOTP, End of Treatment Phase Visit; F/U, Follow-up; Mg, magnesium; P, phosphorus; PRO, patient-reported outcomes; Q3M, every 3 months (every 12 weeks ± 14 days); Q4W, every 4 weeks (± 7 days); SRE, skeletal-related event; V, visit; W, week; wks, weeks.

Section: Appendix A. Schedule of Assessments, Adverse Events Footnote

Replace: Exceptions are hypercalcemia of malignancy, clinical fractures, and SREs, which will be followed until the End of Study (see Sections 7.2.5.1 and 7.2.6).

With: Exceptions are hypercalcemia of malignancy, clinical fractures, and SREs, which will be followed **during LTFU prior to primary analysis data cut-off date** (see Sections 7.2.5.1 and 7.2.6).

Section: Appendix A. Schedule of Assessments, Clinical Fractures / Skeletal-related Events Footnote

Replace: Information about any new clinical fractures (prior to the development of bone metastasis) or skeletal-related events (SREs; defined as any pathologic fracture [vertebral or non-vertebral], radiation therapy to bone [including the use of radioisotopes], surgery to bone, or spinal cord compression following the development of bone metastasis) will be assessed and documented at each scheduled clinic visit and during the follow-up period. Copies of all screening and on-study radiographic assessments performed to diagnose clinical fractures and SREs must be submitted to the central imaging vendor. Copies of all screening and on-study radiology, surgery, or pathology reports should be kept in the subject's records regardless if corresponding radiographs (or equivalent) are available. See Section 7.2.6 for details.

Open-Label Treatment Phase: Radiographic assessments of events incurred during the open label treatment phase will not be submitted to the central imaging vendor.

With: Information about any new clinical fractures (prior to the development of bone metastasis) or skeletal-related events (SREs; defined as any pathologic fracture [vertebral or non-vertebral], radiation therapy to bone [including the use of radioisotopes], surgery to bone, or spinal cord compression following the development of bone metastasis) will be assessed and documented at each scheduled clinic visit and during **LTFU prior to primary analysis data cut-off date**. Copies of all screening and on-study radiographic assessments performed to diagnose clinical fractures and SREs must be submitted to the central imaging vendor. Copies of all screening and on-study radiology, surgery, or pathology reports should be kept in the subject's records regardless if corresponding radiographs (or equivalent) are available. See Section 7.2.6 for details. **After primary analysis data cut-off date: Radiographic assessments of events incurred after primary analysis data cut-off date will not be submitted to the central imaging vendor.**

Section: Appendix A. Schedule of Assessments, PRO Questionnaires (BPI-SF and EQ-5D) Footnote

Delete: ~~Open-Label Treatment Phase: There will be no PRO assessments during the open-label treatment phase.~~

Section: Appendix A. Schedule of Assessments, Imaging Assessments Footnote

Add: Copies of all screening and on-study radiology, surgery, or pathology reports should be kept in the subject's records regardless if corresponding radiographs (or equivalent) are available. **All scheduled imaging will cease after the primary analysis data cut-off date.**

Section: Appendix A. Schedule of Assessments, Imagine Assessments Footnote

Delete: ~~Open-Label Treatment Phase: There will be no scheduled imaging assessments during the open-label treatment phase.~~

Section: Appendix A. Schedule of Assessments, Urine Collection Footnote

Delete: ~~Open-Label Treatment Phase: There will be no scheduled urine collection during the open-label treatment phase.~~

Section: Appendix A. Schedule of Assessments, Anti-denosumab antibodies Footnote

Replace: Serum for anti-denosumab antibody assay will be collected at baseline (prior to administration of the investigational products on study day 1), on study as outlined in the schedule of assessments, at the EOTP visit, and approximately 6 months (24 weeks ± 14 days) after the last investigational product administration.

With: Serum for anti-denosumab antibody assay will be collected at baseline (prior to administration of the investigational products on study day 1) **and** on study as outlined in the schedule of assessments.

Section: Appendix A. Schedule of Assessments, Blood Biomarkers and BSAP Footnote

Delete: ~~Open-Label Treatment Phase: There will be no scheduled biomarker and BSAP collection during the open-label treatment phase.~~

Section: Appendix A. Schedule of Assessments, Pharmacokinetics (PK) Footnote

Delete: ~~Open-Label Treatment Phase: After subjects have been unblinded, there will be no scheduled collection of PK samples for subjects, who switch from placebo to open-label denosumab in the open-label treatment phase. Subjects, who switch from blinded denosumab to open-label denosumab will continue PK sampling per the Schedule of Assessments.~~

Section: Appendix A. Schedule of Assessments, Tumor Samples Footnote

Delete: ~~Open-Label Treatment Phase: There will be no tumor sample collection during the open-label treatment phase.~~

Section: Appendix A. Schedule of Assessments, End of Treatment Phase (EOTP) Visit Footnote

Delete: will be completed per Schedule of Assessments (± 14 days), or at any time once an individual subject discontinues study participation (4 weeks [+ 7 days] after the last dose of investigational product). ~~If denosumab is not determined to have a positive benefit/risk profile compared with placebo, then all subjects will complete the EOTP visit 4 weeks (+ 7 days) after their last dose of investigational product.~~

All EOTP assessments must be completed (unless done within the prior 4 weeks), except imaging assessments, which do not need to be repeated if completed within the prior 6 months (ie, 24 weeks). ~~If denosumab is not determined to have a positive benefit/risk profile compared with placebo, then no imaging will be required at the EOTP visit.~~

Section: Appendix A. Schedule of Assessments, Long-term Follow-up Footnote

Replace: Follow-up

Blinded Treatment Phase

After completing the treatment phase of the study (60 months from study day 1; or as specified in Section 7.1.2.3 and Section 7.1.3), subjects will be followed by clinic visit or telephone contact approximately monthly (Q4W ± 7 days) for six months to assess clinical outcomes (SREs, hypercalcemia of malignancy, concomitant medications, breast cancer therapy, patient-reported outcomes [BPI-SF, EQ-5D], disease recurrence status [until documented evidence of bone metastasis] and survival), approximately every 3 months (every 12 weeks ± 14 days) thereafter to assess SREs, hypercalcemia, disease recurrence status and survival (until documented evidence of bone metastasis), and approximately every 6 months (± 1 month) thereafter to assess SREs, hypercalcemia, and survival, for up to 10 years (120 months) from the date of randomization.

Imaging assessments will continue during follow-up per the Schedule of Assessments, until documented evidence of disease recurrence in the bone (per central imaging analysis or biopsy). See Section 7.2.9 for details. Copies of all radiographic assessments documenting first evidence of disease recurrence and first evidence of disease recurrence in the bone, respectively, will be submitted to the central imaging vendor.

One serum sample to evaluate for the presence of anti-denosumab antibodies will be collected approximately 6 months (24 weeks ± 14 days) after the last investigational product administration. In addition, a biomarker sample will be taken at the time of disease recurrence (including both first disease recurrence, and first disease recurrence in the bone, if applicable).

Open-Label Treatment Phase

After completing the open-label treatment phase of the study, subjects will be followed by clinic visit or telephone contact approximately every 3 months (every 12 weeks ± 14 days) to assess disease recurrence status, and survival (until documented evidence of bone metastasis), and approximately every 6 months (± 1 month) thereafter to assess survival, for up to 10 years (120 months) from the date of randomization.

There will be no scheduled imaging assessments during the open-label treatment phase.

One serum sample to evaluate for the presence of anti-denosumab antibodies will be collected approximately 6 months (24 weeks ± 14 days) after the last investigational product administration. In addition, biomarker samples will be taken at the time of disease recurrence (including both first disease recurrence, and first disease recurrence in the bone, if applicable).

Follow-up if Positive Benefit/Risk is Not Determined

If denosumab is not determined to have a positive benefit/risk profile compared with placebo, then all subjects will complete the EOTP visit and enter follow-up for survival (approximately every 6 months for up to 10 years [120 months] from the date of randomization).

One serum sample to evaluate for the presence of anti-denosumab antibodies will be collected approximately 6 months (24 weeks ± 14 days) after the last investigational product administration.

There will be no scheduled imaging assessments, and no other scheduled procedures.

With: **Long-term** Follow-up:

After completing the treatment phase of the study (60 months from study day 1; or as specified in Section 7.1.2.3 and Section 7.1.3), subjects will be **enter LTFU for approximately 5 years (total study duration for an individual subject is up to 10 years from the date of randomization). The study requirements during LTFU are determined by the primary analysis data cut-off date, refer to Section 7.1.4.1 for assessments prior to primary analysis data cut-off date and Section 7.1.4.2 for assessments required after primary analysis data cut-off date.**

Section: Appendix F. Pregnancy Notification Worksheet

Replace:

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (____)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm___/ dd___/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm ___/dd ___/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ___/dd___/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm___/ dd___/ yyyy_____ ☐ Unknown

Estimated date of delivery mm___/ dd___/ yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm___/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm ___/ dd ___/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page 1 of 1

With:

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20060359

Study Design: ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____) _____ **Fax** (____) _____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm ___ / dd ___ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
Denosumab				mm ___ /dd ___ /yyyy ____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ___ /dd ___ /yyyy ____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm ___ / dd ___ / yyyy ____ ☐ Unknown

Estimated date of delivery mm ___ / dd ___ / yyyy ____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm ___ / dd ___ / yyyy ____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm ___ / dd ___ / yyyy ____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

Section: Appendix G. Serious Adverse Event Worksheet/Electronic Serious Adverse Event Contingency Report Form

Delete:

Completion Instructions
Electronic Serious Adverse Event (eSAE) Contingency Reporting Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, do not enter that event into the EDC system (eg, Rave) unless directed to do so by Amgen.

Header Information
Complete either Section A or Section B and follow the instructions provided within the applicable section.

Section A:
Complete this section and complete only page 1 of the SAE Report Form if the EDC system (eg, Rave) is active and your site does not have access for reasons such as: internet connectivity issues, the EDC system is down, etc.

Section B:
Complete this section and complete all pages of the SAE Report Form if:
- You are submitting a screening serious adverse event report and the database is not active yet
- You are submitting a serious adverse event report and your site access has been removed

1. **Site Information**

Site Number – Enter your assigned site number for this study

Investigator, Country, Reporter, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

Subject ID Number – Enter the entire number assigned to the subject

Date of Birth, Sex, and Race – Enter the subject's demographic information

End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

Provide the date the Investigator became aware of this Serious Adverse Event Information

Serious Adverse Event Diagnosis or Syndrome –
- If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
- If a diagnosis is not known, the relevant signs/symptoms meeting serious criteria should be entered.
- If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

Date Started* – Enter date the adverse event first started; not when the event met serious criteria, when a diagnosis was made or when the subject was hospitalized. **This is a mandatory field.**

Date Ended – Enter date the adverse event ended, not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

If event occurred before the first dose of IP, add a check mark in the corresponding box.

Serious Criteria Code* – This is a mandatory field. Enter all reasons why the reported event has met serious criteria:
- Immediately life-threatening – Use only if the subject was at **immediate** risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criteria.

Relationship* – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
- Resolved – End date is known
- Not resolved / Unknown – End date is unknown
- Fatal – Event led to death

If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant administration – only diagnostic tests or activities mandated by the protocol.

If you completed Section A of the form header, stop here, complete the signature section at the bottom of page 1 and fax the form to Amgen. Otherwise, complete the remainder of the form. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

FORM-056006 eSAE Contingency Reporting Form *Version 2.0 Effective Date 07-May-2012*
Page 1 of 2

Completion Instructions
Electronic Serious Adverse Event (eSAE) Contingency Reporting Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, do not enter that event into the EDC system (eg, Rave) unless directed to do so by Amgen.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

4. **Hospitalization**
   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

5. **Investigational Product Administration**

   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label

   Initial Start Date – Enter date the product was first administered, regardless of dose.

   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.

   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.

   Action Taken with Product – Enter the status of the product administration.

6. **Relevant Concomitant Medications**

   Indicate if there are any relevant medications.

   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other relevant medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

   Co-suspect – Indicate if the medication is co-suspect in the event

   Continuing – Indicate if the subject is still taking the medication

   Event Treatment – Indicate if the medication was used to treat the event

7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. **Relevant Laboratory Tests**

   Indicate if there are any relevant laboratory values.

   For each test type, enter the test name, units, date the test was run and the results.

Provide your Site Number and the Subject ID Number in the designated section at the top of Page 3.

9. **Other Relevant Tests**

   Indicate if there are any tests, including any diagnostics or procedures.

   For each test type, enter the date, name, results and units (if applicable).

10. **Case Description**

    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

Section: Appendix K. Lactation Notification Worksheet

Replace:

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# select

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (_____)_____ Fax (_____)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2. Page 1 of 1

With:

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20060359

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
Denosumab				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm_____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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REFERENCES

Cheng L, Swartz MD, Zhao H, et al. Hazard of recurrence among women after primary breast cancer treatment - a 10-year follow-up using data from SEER-medicare. *Cancer Epidemiol Biomarkers Prev.* 2012;21(5):800-809.

Demicheli R, Abbattista A, Miceli R, Valagussa P, Bonadonna G. Time distribution of the recurrence risk for breast cancer patients undergoing mastectomy: further support about the concept of tumor dormancy. *Breast Cancer Res Treat*. 1996;41(2):177-185.

Amendment # 3

Protocol Title: 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)

Amgen Protocol Number (Denosumab) 20060359

IND # 9838

EudraCT number 2009-011299-32

Amendment Date: 18 March 2015

Rationale:

The main purpose of this protocol amendment is to add disease-free survival (DFS) in the postmenopausal subset as a secondary endpoint based on recently published data supporting an enhanced treatment effect of adjuvant bisphosphonates in postmenopausal subjects with early breast cancer.

Additional changes to the study protocol are summarized below:

- A summary of recent literature was included in the background section to support adding DFS in postmenopausal women as a secondary endpoint.
- The hazard ratio of denosumab compared with placebo was added for the postmenopausal subset.
- Pathological variables in tumor tissue from neoadjuvant subjects after surgery was added as an exploratory objective, as a large proportion of the enrolled subjects are neoadjuvant, where pathologic evaluation after surgery is of importance.
- The numbers of subjects with events (any disease recurrence or died, whichever comes last) required for the interim and final analyses was updated to account for event rates.
- The period of time for which subjects must not become pregnant or breastfeed following the end of treatment was changed from 7 months to 5 months, in accordance with Investigator's Brochure and Informed Consent Form updates.
- Clarification was made in the language describing study duration for individual participants, frequency of follow-up visits, and visit windows, to facilitate study conduct.

- The duration of the study was changed based on the change in the expected/projected time to primary analysis.
- Section 9.1.3 was updated to also include atypical femoral fracture along with osteonecrosis of the jaw as adverse events of interest which should undergo adjudication by an independent panel of experts.
- Covariates which may be explored in relation to the primary and secondary efficacy endpoints were updated, and primary tumor size and lymph node status were added to the list of covariates, as these are important prognostic factors.
- The expected event rates at 3 years for bone metastasis-free survival (BMFS) and DFS were updated.
- The Key Sponsor Contact (Global) information was updated
- Minor editorial changes or clarifications were made throughout the protocol for consistency between sections, to facilitate study conduct, or to correct typographical errors.

Amendment 2

Protocol Title: 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)

Denosumab (AMG 162)

Amgen Protocol Number (Denosumab) 20060359
IND # 9838

EudraCT number 2009-011299-32

Amendment Date: 15 August 2012

Rationale:

The purpose of this amendment is to extend the collection of skeletal related event (SRE) information through the long-term follow-up. Objectives and endpoints for SREs and bone metastasis were also modified.

Additional changes to the study are summarized below:

- The fasting requirement has been removed from the urine collection for uNTx
- The reporting timeframe for Serious Adverse Events (SAE) has been changed from 1 day to 24 hours
- The SAE reporting section has been updated to reflect the use of electronic SAE reporting
- Pregnancy and Lactation Surveillance Programs have been added to section 9
- Typographic and formatting errors, redundancies, and inconsistencies were corrected.

Amendment 1

Protocol Title: 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)

Denosumab (AMG 162)

Amgen Protocol Number (Denosumab) 20060359
IND # 9838

EudraCT number 2009-011299-32

Amendment Date: 05 May 2011

Rationale:

The purpose of this amendment is to increase the window for screening imaging assessments to document disease extent from 12 weeks to 24 weeks. This increase in the screening window will allow subjects additional time to complete all screening imaging assessments required for participation in the study.

Additionally, in consideration of the length of time anticipated to reach the primary analysis date, a second formal interim analysis is being added.

The amount of time expected to reach the primary analysis data cut-off date has been modified from 75 months to 77 months resulting in a change in the overall event rate from approximately 730 subjects to 735 subjects who have developed bone metastasis or died, and approximately 910 subjects to 922 subjects who have developed any disease recurrence or died, whichever comes last.

Additional changes to the study are summarized below:

- The number of centers is being increased from 400 to 500 sites globally
- Breast density measurements have been included as an exploratory outcome (objective and endpoint) for the study. These assessments will be performed by the central imaging laboratory based on protocol-specified annual mammograms. No additional imaging will be required.
- Certain study-related definitions have been clarified including a change to the end of study from the end of the treatment phase to the last assessment by the last subject. This change in definition does not affect the overall timing or conduct of the study.
- Appendix C from the original protocol has been removed and replaced with an Investigational Product Instruction Manual. Other appendices have been adjusted to accommodate this change.
- Typographic and formatting errors, redundancies, and inconsistencies were corrected.