A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study to Determine the Treatment Effect of Denosumab in Subjects With Non-Metastatic Breast Cancer Receiving Aromatase Inhibitor Therapy

Denosumab

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15 July 2019 Amendment 6 (added zoledronic acid substudy)

Investigator's Agreement

I have read the attached protocol entitled "A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study to Determine the Treatment Effect of Denosumab in Subjects with Non-Metastatic Breast Cancer receiving Aromatase Inhibitor Therapy" dated **15 July 2019**, 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 and applicable European Union and FDA regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56 and 312.

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)

before study initiation, during the study if there are changes that affect my financial disclosure status, and after the study is completed.

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.

_____
Signature

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

Protocol Synopsis

Title: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study to Determine the Treatment Effect of Denosumab in Subjects with Non-Metastatic Breast Cancer Receiving Aromatase Inhibitor Therapy

Study Phase: Phase 3

Indication: Treatment of therapy-induced bone loss to reduce occurrence of fractures in patients undergoing estrogen deprivation therapy.

Primary Objective:

To determine whether denosumab compared to placebo will reduce the rate of first (on-study) clinical fracture (ie, clinically evident fracture with associated symptoms) in women with non-metastatic breast cancer receiving non-steroidal aromatase inhibitor therapy (AIT).

Secondary Objective(s):

To assess the effect of denosumab compared to placebo on the following:

Fracture-related secondary endpoints:

- Bone mineral density (BMD) at lumbar spine, total hip and femoral neck in a subgroup of subjects at pre-selected sites
- Incidence of new vertebral fractures (both clinical and morphometric [ie, a fracture in the vertebral column that is not clinically evident and that is asymptomatic])
- Incidence of new or worsening of pre-existing vertebral fractures (both clinical and morphometric)

Disease outcome-related secondary endpoints:

- Disease-free survival (DFS)
- Bone metastasis-free survival (BMFS)
- Overall survival (OS)
- To assess the safety and tolerability of denosumab in this population

Exploratory Objective(s):

[redacted]

Hypotheses:

Clinical Efficacy Hypothesis:

Denosumab, when administered subcutaneously (SC) at a dose of 60 mg every 6 months (Q6M), will be considered efficacious in breast cancer subjects receiving AIT if the rate of first clinical fractures in denosumab-treated subjects is lower than that in placebo-treated subjects. It is anticipated that denosumab will reduce the rate by 30% compared with placebo (ie, the true hazard ratio of denosumab compared with placebo is 0.70).

Clinical Safety Hypothesis:

Denosumab, when administered SC at a dose of 60 mg Q6M, will be well tolerated in breast cancer subjects receiving AIT.

Study Design:

This is a multi-center phase 3, randomized, double-blind, placebo-controlled study to determine the treatment effect of denosumab in subjects with breast cancer treated with an approved non-steroidal aromatase inhibitor (AI), (eg, anastrazole). Approximately 3400 subjects will be randomized in a 1:1 ratio to receive either denosumab administered at a dose of 60 mg or placebo SC Q6M in a blinded manner. Subjects will be recruited over approximately 82 months. The randomization schedule will be stratified by: type of hospital (pre-selected centers or other centers), prior AI usage (Y/N) and total lumbar spine BMD score at baseline (T-score < –1.0 vs ≥ -1.0).

Subjects will remain on investigational product (IP) until the primary analysis data cut-off date (PADCD) is reached, which is defined as the time at which the required number of events (where an event is defined as first clinical fracture) is reached and all subjects had the opportunity to receive at least 2 doses of IP, whichever occurs later. When the PADCD date is reached, all subjects will discontinue IP.

For all subjects, whose last regular study visit within 6 months (+ 45 days time window) prior to the PADCD was a yearly visit (eg, month 12, 24, etc) and radiological assessments were performed, this visit will be considered an end of treatment (EOT) visit (corresponding case report form [CRF] will have to be completed). For those subjects, the next visit will be regarded as a long-term follow-up (LTFU) visit, at which an antibody sample will be taken. Those subjects, for whom the radiological assessments were not performed, will need to attend the next scheduled 6 months visit, when radiological assessments (vertebral x-rays, dual X-ray absorptiometry [DXA]) will take place and an antibody sample will be taken. For these subjects this visit will be considered as EOT visit.

It is highly recommended that all subjects should receive at least 500 mg elemental calcium and at least 400 IU vitamin D daily throughout treatment with IP. If a subject has greater than 10% loss of BMD at the total hip or lumbar spine over any 1-year period, then an informed discussion between the investigator and the subject regarding alternative therapies and appropriate treatment is required.

The number of primary endpoint events observed will drive the timing of the primary and final analyses. The actual timing of the primary analysis will depend on the subject enrollment rate and the rate at which clinical fractures are observed.

All subjects, whose last regular study visit within 6 months (+ 45 days time window) prior to the PADCD was a 6 months visit (eg, month 6, 18, etc), will have to attend the next regularly scheduled yearly study visit (eg, month 12) within 6 months after PADCD at the latest and perform all corresponding assessments, including antibody sampling.

Data on fractures occurring between the last visit prior to PADCD and PADCD have to be collected via telephone or physical visits within 6 months after PADCD at the latest.

Subjects who withdraw from IP prior to the observed PADCD will continue to attend Q6M study visits for assessment of the primary and secondary end-point and safety.

Subjects completing or discontinuing AIT will have the opportunity to remain on IP for at least 2 doses of IP after their last scheduled study visit during which they were still on AIT. Following the study PADCD, subjects will be followed for DFS, BMFS, and OS every 12 months (Q12M) by clinic visits or telephone contacts starting from their last study visit (considered as EOT visit) until a maximum of either 18 or 66 months after the PADCD, depending on an interim analysis at PADCD (see Sections 7.16 and 10.5). Based on the Data Monitoring Committee (DMC) recommendation that interim futility analysis of DFS did not indicate futility, it was decided to follow subjects until a maximum of approximately 66 months after PADCD. Following regulatory and Institutional Review Board / Independent Ethics Committee (IRB/IEC) approval of Protocol Amendment 4, further data will be assessed (see Section 3.1).

Due to the statistically significant treatment effect in the primary endpoint and fracture-related secondary endpoints between the denosumab arm and the placebo arm, which were demonstrated at the primary analysis (Gnant et al.; Lancet 2015 [see Section 2.3]), willing and

eligible subjects randomized to placebo during the double-blind phase may participate in an open-label phase (OLP) and receive denosumab 60 mg Q6M for up to 36 months (maximum of 7 doses), as recommended by the DMC.

After regulatory and IRB/IEC approval of Protocol Amendment 4, the opportunity to start open-label denosumab will open for a 12-month period. Subjects who consent and fulfil the eligibility criteria will receive denosumab 60 mg Q6M for up to 36 months (a maximum of 7 doses), as recommended by the DMC. Subjects who do not fulfil the eligibility criteria or do not consent will complete LTFU assessments only (Appendix A).

Subjects who do not receive open-label denosumab will be followed once a year (Q12M study visit) by clinic visits or telephone contacts for:

- DFS, BMFS, and OS
- Clinical fracture recording (including serious adverse event [SAE] reporting of suspected atypical femoral fracture cases)
- Concomitant bone affecting medication
    - Bone targeted therapy (eg, bisphosphonate or denosumab)
    - Glucocorticoids
    - Antiepileptic drugs
    - Antidepressants
    - Insulin
- Anti-cancer related therapy (eg, chemotherapy or endocrine therapy)
- Supplements (vitamin D and calcium)

Subjects who receive open-label denosumab will attend clinic visits Q6M for:

- Administration of denosumab (60 mg SC)
- Collection of serious and non-serious adverse events [(S)AEs] of special interest (oral events) and SAEs
- Clinical fracture recording (including SAE reporting of suspected atypical femoral fracture cases) (Q12M only)
- DFS, BMFS, and OS (Q12M only)
- Concomitant bone affecting medication (Q12M only)
    - Bone targeted therapy (eg, bisphosphonate or denosumab)
    - Glucocorticoids
    - Antiepileptic drugs
    - Antidepressants
    - Insulin
- Anti-cancer related therapy (eg, chemotherapy or endocrine therapy) (Q12M only)
- Supplements (vitamin D and calcium) (Q12M only)

In addition, for all subjects, BMD data will be collected at any time a DXA scan is performed for BMD analysis as standard of care **(SOC)** from PADCD to end of study **(EOS)**; these data will be collected in the CRF.

In the event a serious or non-serious adverse event of special interest (oral event) or other SAE is identified outside the subjects' scheduled visits, the standard guidance in Section 9 should be followed.

A time-driven analysis for efficacy of the secondary endpoint DFS will take place approximately 18 months after PADCD, prior to any unblinding of subjects at the investigator/subject level.

At the end of the **main** study **(LTFU and OLP)**, a final analysis will occur looking at the secondary disease outcome-related endpoints (OS and BMFS) as well as an exploratory analysis of [redacted]

[redacted]. **Data collected during the ZA substudy will be censored at the End of Open-label Treatment Visit or the EOS Visit (LTFU and OLP), whichever occurs later, for the final analysis.**

A study schema at the end of the protocol synopsis section describes the overall main study design.

Zoledronic Acid (ZA) Substudy:

A substudy has been added in Appendix G to evaluate subjects completing open-label denosumab treatment, to either receive a single dose of ZA, or to be managed according to current standard of care (SOC) for the patient population.

Subjects enrolled in the main study who received denosumab during the open label phase and are deemed eligible per the inclusion and exclusion criteria, may choose to participate in this substudy. Subjects that are not included in the substudy will end study as planned. Protocol-defined denosumab administration will complete at end of the open-label period no matter if subjects participate in the substudy or not.

Subjects enrolled in the substudy will be randomized to either receive a single dose of ZA (Therapy Arm) or will be managed according to the current SOC for this patient population (Control Arm). Day 1 for both arms is 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit. Follow up will continue for a total of 18 months after day 1.

Primary Endpoints:

- The time to the first clinical fracture

Secondary Endpoints:

Fracture-related secondary endpoints:

- The percent change in total lumbar spine, total hip and femoral neck BMD from baseline to 36 months (at pre-selected sites)
- Subject incidence of new vertebral fractures (morphometric vertebral fractures identified from on study x-rays and clinical vertebral fractures confirmed by x-rays) at month 36
- Subject incidence of a new or worsening of pre-existing vertebral fractures (morphometric vertebral fractures identified from on study x-rays and clinical vertebral fractures confirmed by x-rays) at month 36

Disease outcome-related secondary endpoints:

- Disease-free survival determined by the time from randomization to the first observation of disease recurrence or death from any cause
- Bone metastasis-free survival determined by the time from randomization to the first observation of bone metastasis or death from any cause
- Overall survival determined by the time from randomization to death from any cause

Safety Endpoints:

- Subject incidence of treatment-emergent adverse events
- Clinically significant changes in laboratory values
- Subject incidence of anti-denosumab antibody (binding and neutralizing) formation

Sample Size:

Approximately 3400 subjects will be enrolled in this study (1700 in each arm)

Summary of Subject Eligibility Criteria (double-blind phase):

Inclusion criteria:

- Histologically or cytologically confirmed adenocarcinoma of the breast
- Female subjects with non-metastatic disease who are estrogen receptor and/or progesterone receptor positive, and who have completed their treatment pathway (surgery, chemotherapy)
- Subjects who are currently on, or will initiate an approved non-steroidal aromatase inhibitor therapy (eg, anastrazole) in the adjuvant setting
- Postmenopausal woman[1,2,] defined as a woman fulfilling any 1 of the following criteria:
  - Having undergone a bilateral oophorectomy;
  - Age ≥ 60 years;
  - Aged < 60 years meeting the following requirements:
    - Follicle-stimulating hormone and estradiol in the postmenopausal range
    - A negative pregnancy test within 7 days prior to randomization. Subjects who have undergone a hysterectomy do not require a pregnancy test.
- Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1
- Before any study-specific procedure is performed, a signed and dated written informed consent must be obtained

Exclusion criteria:

- Aromatase inhibitor therapy for more than 24 months
- Prior or concurrent treatment with Selective Estrogen Receptor Modulators (eg, tamoxifen)
- Evidence of metastatic disease
- Current or prior intravenous bisphosphonate administration
- Oral bisphosphonate treatment:
  - Greater than or equal to 3 years continuously
  - Greater than 3 months but less than 3 years unless subject has had a washout period of at least 1 year
  - Any use during the 3-month period prior to randomization
- Known liver or renal deficiency as determined by the investigator and indicated by the following criteria:
  - Aspartate aminotransferase ≥ 2.5 x upper limit of normal (ULN)
  - Alanine transaminase ≥ 2.5 x ULN
  - Serum creatinine ≥ 2 x ULN
- Prior administration of denosumab (AMG 162)
- Recurrence of the primary malignancy (eg, during the allowed interval of pretreatment with an aromatase inhibitor)
- Diagnosis of any second non-breast malignancy within the last 5 years, except for adequately treated basal cell or squamous cell skin cancer, or for in situ carcinoma of the cervix uteri
- Known history of any of the following conditions either by subject self report or chart review
  - Paget's disease (bone), Cushing's disease, hyperprolactinemia, or other active metabolic bone disease

[1] For subjects previously treated with a luteinizing hormone-releasing hormone antagonist, the last dose must have been 4 months prior to randomization and follicle-stimulating hormone and estradiol must be in the postmenopausal range.

[2] Subjects who have received adjuvant or neoadjuvant chemotherapy must have met 1 of the criteria for postmenopausal status prior to that chemotherapy.

  - Hypercalcemia or hypocalcemia: as defined by calcium outside the normal range (A single value outside the normal range does not necessarily constitute hypercalcemia or hypocalcemia, but should be 'corrected' before including the subject. Subjects with a known history of hypercalcemia or hypocalcemia cannot be included.)
  - Major surgery, or significant traumatic injury occurring within 4 weeks prior to randomization
  - Known Human Immunodeficiency Virus infection
  - Active infection with hepatitis B or hepatitis C virus
- 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
- Thirty days or less since receiving an investigational product or device in another clinical study
- Known sensitivity to any of the products to be administered during the study (eg, mammalian-derived products, calcium or vitamin D)
- Subjects who are pregnant, breastfeeding, or plan to become pregnant during the course of the study. All subjects with reproductive potential must have a negative pregnancy test within 7 days before randomization.
- Any kind of disorder that compromises the ability to give written informed consent and/or comply with study procedures

Subjects randomized to placebo during the double-blind phase may be eligible to receive denosumab in the OLP. Please refer to Sections 4.3 and 4.4 for eligibility criteria for receiving denosumab in the OLP.

Investigational Product Dosage and Administration in Double-blind Phase and in the OLP:

Denosumab 60 mg administered SC every 6 months

Control Group (double-blind phase):

Matching placebo administered SC every 6 months

Procedures:

Blinded Treatment Phase

Written informed consent must be obtained from all subjects prior to screening for eligibility.

Screening assessments will include a medical and medication history, physical examination (ECOG performance status), weight, height and vital signs (temperature, pulse, blood pressure), lateral spine radiographs, bone scan, DXA and collection of blood for hematology, chemistry, pregnancy test (if applicable) and denosumab antibody analysis.

Eligible subjects will be randomized into 1 of the 2 treatment groups within 35 days of screening. First administration of IP (day 1) must take place within 8 days of randomization. During this visit the baseline related assessments will be completed. After the initial dose of IP is administered, subjects will return for study visits and receive IP every 6 months. The treatment phase will end when the PADCD is reached (see Glossary). At the end of the treatment phase all subjects will discontinue IP.

For all subjects, whose last regular study visit within 6 months (+ 45 days time window) prior to the PADCD was a yearly visit (eg, month 12, 24, etc) and radiological assessments were performed, this visit will be considered an EOT visit (corresponding CRF will have to be completed). For those subjects, the next visit will be regarded as LTFU visit, at which an antibody sample will be taken. Those subjects, for whom the radiological assessments were not performed, will need to attend the next scheduled 6 months visit, when radiological assessments (vertebral x-rays, DXA) will take place and an antibody sample will be taken. For these subjects this visit will be considered as EOT visit.

All subjects, whose last regular study visit within 6 months (+ 45 days time window) prior to the PADCD was a 6 months visit (eg, month 6, 18, etc), will have to attend the next regularly scheduled yearly study visit (eg, Q12MV) within 6 months after PADCD at the latest and perform all corresponding assessments, including antibody sampling.

Data on fractures occurring between the last visit prior to PADCD and PADCD have to be collected via telephone or physical visits within 6 months after PADCD at the latest.

Subjects who withdraw early from investigational product will continue on study, without investigational product administration according to the Schedule of Assessments (Appendix A). Subjects completing or discontinuing AIT will have the opportunity to remain on IP for at least 2 doses of IP after their last scheduled study visit during which they were still on AIT.

The following procedures will be performed per the schedule outlined in Appendix A: physical exam, weight and vital signs, lateral spine radiographs, DXA scans, blood draw for hematology, and serum chemistry. Clinical and morphometric fracture events will be recorded throughout the study as described in Section 7.7. Adverse events and concomitant medications will be recorded through 30 days after the last dose of investigational product. Denosumab antibody level will be assessed at screening and the End of Treatment visit.

Open-label Phase

Subjects randomized to placebo during the double-blind phase may receive denosumab in the OLP. The opportunity to start open-label denosumab will be open for 12 months following Protocol Amendment 4 regulatory and IRB/IEC approval.

Subjects currently taking an approved non-steroidal AI (eg, anastrazole), or who have completed or discontinued AIT within 12 months prior to participation in the OLP will be eligible to receive up to 36 months (maximum of 7 doses) of denosumab. For details of eligibility see Sections 4.3 and 4.4.

Informed consent must be obtained before unblinding to confirm eligibility. Please refer to Appendix A (Schedule of Assessments) for a detailed list of OLP procedures.

Long-term Follow-up

Following the study PADCD, all subjects will be followed for DFS, BMFS, and OS every 12 months by clinic visits or telephone contacts starting from their last study visit (considered as EOT visit) until approximately 66 months after the PADCD.

Following regulatory approval of Protocol Amendment 4 further data will be assessed.

Subjects who do not receive open-label denosumab will be followed once a year (Q12M study visit) by clinic visits or telephone contacts for:

- DFS, BMFS, and OS
- Clinical fracture recording (including SAE reporting of suspected atypical femoral fracture cases)
- Concomitant bone affecting medication:
    - Bone targeted therapy (eg, bisphosphonate or denosumab)
    - Glucocorticoids
    - Antiepileptic drugs
    - Antidepressants
    - Insulin
- Anti-cancer related therapy (eg, chemotherapy or endocrine therapy)
- Supplements (vitamin D and calcium)

Subjects who receive open-label denosumab will attend clinic visits Q6M for:

- Administration of denosumab (60 mg SC)
- Collection of (S)AEs of special interest (oral events) and SAEs
- Clinical fracture recording (including SAE reporting of suspected atypical femoral fracture cases) (Q12M only)
- DFS, BMFS, and OS (Q12M only)
- Concomitant bone affecting medication (Q12M):
    - Bone targeted therapy (eg, bisphosphonate or denosumab)
    - Glucocorticoids
    - Antiepileptic drugs
    - Antidepressants
    - Insulin
- Anti-cancer related therapy (eg chemotherapy or endocrine therapy) (Q12M only)
- Supplements (vitamin D and calcium) (Q12M only)

In addition, for all subjects, BMD data will be collected at any time a DXA scan is performed for BMD analysis as standard of care from PADCD to end of study; these data will be collected in the CRF.

In the event a serious or non-serious adverse event of special interest (oral event) or other SAE is identified outside the subjects' scheduled visits, the standard guidance in Section 9 should be followed.

Statistical Considerations:

This study is designed to compare the treatment effect of denosumab with placebo in the rate of clinical fracture in women with breast cancer receiving AIT.

Approximately 3400 subjects will be randomized in a 1:1 ratio to receive denosumab or placebo. The randomization will be stratified by type of hospital, prior AI usage and total lumbar spine BMD score (T-score < -1.0 vs ≥ -1.0). The treatment phase will end when approximately 247 subjects have experienced their first clinical fracture and all subjects have had the opportunity to receive at least 2 doses of IP when the primary analysis will be conducted.

The primary analysis of the time to first on-study clinical fracture will use a Cox model (Cox, 1972) including treatment groups as the independent variable and stratified by the randomization stratification factors. The secondary endpoints subject incidence of new vertebral fractures and subject incidence of new or worsening pre-existing vertebral fractures will use logistic regression models including treatment groups as the independent variable and stratified by the randomization stratification factors. Analysis of the percent change in lumbar spine, total hip and femoral neck from baseline to month 36 at pre-selected sites will be analyzed using a mixed effect model including treatment groups as the independent variable and stratified by the randomization stratification factors. A time-driven analysis for efficacy of the secondary endpoint DFS will take place approximately 18 months after PADCD, before unblinding of subjects at the investigator/subject level has occurred.

At the end of the **main** study **(LTFU and OLP)**, a final analysis will occur looking at the secondary disease outcome-related endpoints (OS and BMFS) as well as an exploratory analysis [redacted] **for the main study**. [redacted] **Only data collected up to the EOS visit (end of OL treatment visit or their last scheduled LTFU visit) will be included in the final analysis. Any data collected from the ZA substudy will be excluded.**

The primary and secondary null hypothesis (percent change in BMD endpoints, incidence of new vertebral fractures at month 36 and incidence of new or worsening pre-existing vertebral fractures

at month 36) will be tested using the hierarchical analysis strategy and the Hochberg procedure to control the overall significance level of 0.05.

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

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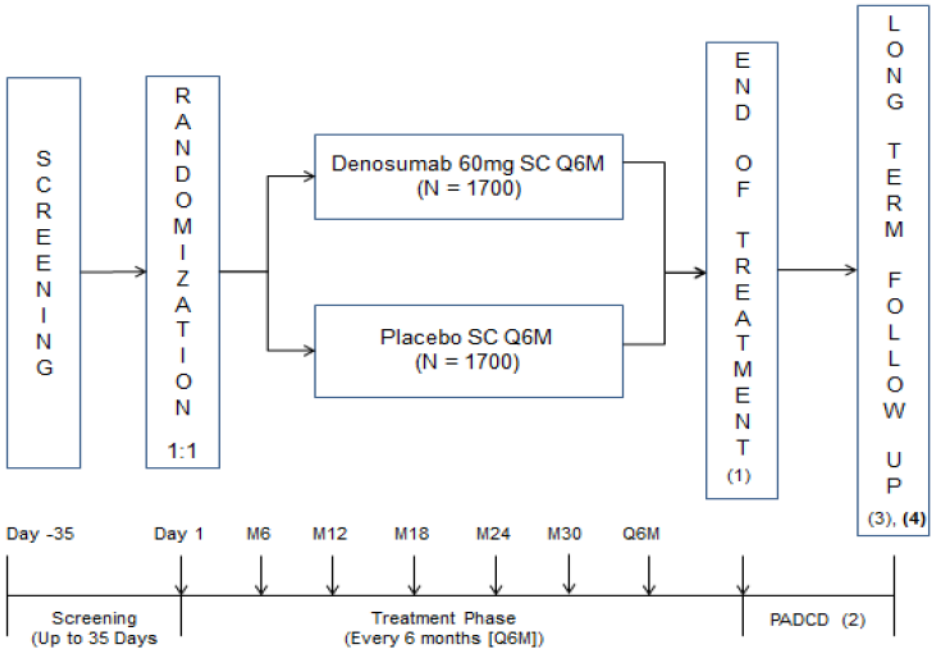
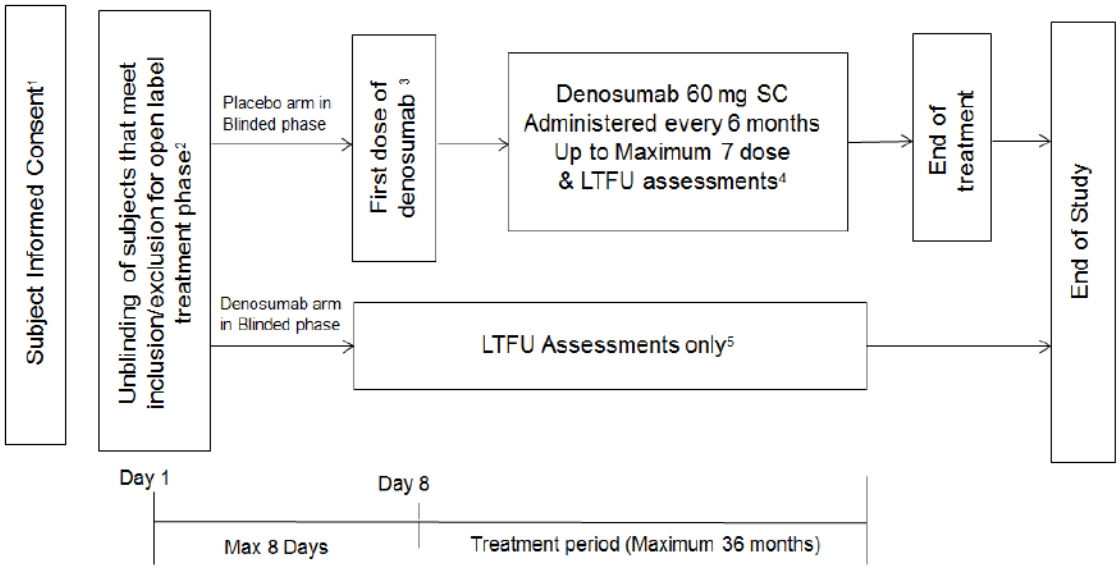
Double-blind Phase - Study Design and Treatment Schema



1. End of Treatment– At PADCD, the last yearly visit will be considered the End of Treatment (EOT) visit. Subjects will undergo EOT assessments as follows: For all subjects, whose last regular study visit within 6 months (+ 45 days time window) prior to the PADCD was a yearly visit (eg, month 12, 24, etc), this visit will be considered an end of treatment (EOT) visit. An antibody sample will be taken during the first visit of the Long-Term Follow Up. All subjects whose last regular study visit within 6 months (+ 45 days time window) prior to the PADCD was a 6 months visit (eg, month 6, 18, etc), will have to attend the next regularly scheduled yearly study visit (eg, Q12M) within 6 months after PADDC at the latest and perform all corresponding assessments, including antibody sampling. Subjects who withdraw from IP prior to the PADCD will continue to attend Q6M study visits for assessment of the primary and secondary end-point and safety until PADCD and will then enter the Long-Term Follow-Up; and subjects who withdraw full consent (=EOS) will have no further study assessments from that date forward.
2. Primary analysis Data Cut Off Date (PADCD) – the date when approximately 247 subjects have experienced their first clinical fracture and all subjects have either withdrawn or had the opportunity to receive at least 2 doses of IP.
3. Subjects will be followed for disease-free survival (DFS), bone metastasis-free survival (BMFS), and overall survival (OS) once every 12 months (Q12M) by clinic visits or telephone contacts starting from their last study visit (considered as EOT visit) until **approximately** 66 months after the PADCD.
4. **After regulatory and IRB/IEC approval of Amendment 4, the opportunity to start open label denosumab will open for a 12 month period. Subjects who consent and fulfil the eligibility criteria will receive denosumab in the OLP for up to 36 months (a maximum of 7 doses). Subjects who do not fulfil the eligibility criteria or do not consent will complete LTFU assessments only (Appendix A).**

Open-label Phase - Study Design and Treatment Schema



1. Enrolment into the open label phase will be open for one year following regulatory approval of protocol amendment 4.
2. Unblinding can only occur at the next scheduled visit following disease outcome-related endpoint analysis at 18 months PADCD.
3. First dose of denosumab must occur within 8 days of unblinding.
4. Subjects receiving treatment in the open label phase will be followed for approximately 66 months after PADCD or until the end of treatment, whichever is longer.
5. Subjects not receiving treatment in the open label phase will be followed for approximately 66 months after PADCD.

Study Glossary

Abbreviation/Acronym	Definition
ABCSG	Austrian Breast and Colorectal Cancer Study Group
AE	Adverse Event
AIT	aromatase inhibitor therapy
ATAC	Arimidex, Tamoxifen Alone or in Combination
BIG	Breast International Group
BMD	bone mineral density
BMFS	Bone metastases-free survival
CI	confidence interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTX	**C-terminal telopeptide**
DMC	Data Monitoring Committee
DFS	Disease-free survival
DXA	Dual X-Ray Absorptiometry
ECOG	Eastern Cooperative Oncology Group
EOS	end of study
EOT	End of treatment
ER	estrogen receptor
FAS	full analysis set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HER-2	Human Epidermal growth factor Receptor 2
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional Review Board
IV	intravenous

Abbreviation/Acronym	Definition
IVRS	interactive voice response system
LTFU	Long-term follow-up
M	**month(s)**
MedDRA	Medical Dictionary for Regulatory Activities
OL	**open-label**
OLP	open-label phase
ONJ	osteonecrosis of the jaw
OS	Overall survival
PADCD	primary analysis data cut-off date
PFS	prefilled syringe
PgR	progesterone receptor
PIN	personal identification number
Q6M	every 6 months
Q12M	every 12 months
RANK/L	receptor activator for nuclear factor kappa B ligand
SAE	Serious Adverse Event
(S)AE	serious and non-serious adverse event
SERM	Selective Estrogen Receptor Modulator
SC	Subcutaneous
SmPC	**summary of product characteristics**
ULN	upper limit of normal per laboratory reference range
ZA	**zoledronic acid**

Study Term	Definition
Clinical fracture	clinically evident fracture with associated symptoms
Date of randomization	date subject is randomized; enrollment date
Day 1 **in double-blind phase and OLP**	first day investigational product is administered
Day 1 in ZA substudy	**Defined as 8 months (± 4 weeks) after the last OLP denosumab dose** **For treatment arm: first day ZA is administered** **For control arm (SOC treatment): SOC day 1 visit**
End of Open-Label Treatment	last administration of open-label phase denosumab for each subject
End of Open-Label Treatment Visit	the last assessment of the protocol specified open-label treatment for a subject. **If not eligible for ZA substudy or willing to take part in this substudy, subjects will complete an end of OL treatment visit 30 to 45 days after the last dose of OL denosumab either by clinic visit or telephone contact.**
End of study (EOS)	the date when the last subject completes the last scheduled visit
End of Study visit	a subject's last formal visit or last formal contact or an unscheduled study visit in case of early withdrawal from study
End of Study (EOS) of ZA substudy	**The date when the last subject participating in the ZA substudy completes the last formal visit or an unscheduled study visit in case of early withdrawal from the ZA substudy**
End of Treatment **in double-blind phase**	last administration of double-blind investigational product for each subject
End of Treatment visit **in double blind phase**	the visit at which the subject receives the last dose of IP; for all subjects, whose last regular study visit within 6 months (+ 45 days time window) prior to the PADCD was a yearly visit (eg, months 12, 24, etc) and radiological assessments were performed, this visit will be considered an EOT visit. Those subjects, for whom the radiological assessments were not performed, will need to attend the next scheduled 6 months visit, when radiological assessments (vertebral x-rays, DXA) will take place and an antibody sample will be taken. For these subjects this visit will be considered as EOT visit. For those whose last regular study visit within 6 months (+ 45 days time window) prior to the PADCD was a 6 months visit (eg, month 6, 18, etc), the next regularly scheduled yearly study visit (eg, Q12M) within 6 months after PADCD will be considered an EOT visit
Enrollment date	date of randomization
Final analysis	analysis performed after long-term follow up, **and OLP,**
Interim Analysis	An interim analysis for futility for the secondary endpoint DFS will be performed after PADCD by an independent statistician

Study Term	Definition
Long-Term Follow-Up (LTFU) visit	all Q12M visits that are attended after EOT visit
Morphometric fracture	a fracture in the vertebral column that is not clinically evident and that is asymptomatic
Primary analysis	analysis at Primary Analysis Data Cut-off Date (PADCD)
SOC	**standard of care**
Screening period	begins with signed informed consent and ends on day investigational product is administered
Primary Analysis Data Cut-off Date (PADCD)	the date when approximately 247 subjects have experienced their first clinical fracture and all subjects have either withdrawn or had the opportunity to receive at least 2 doses of IP.
ZA substudy Treatment	**Subjects randomized to treatment arm will receive a single dose ZA.**

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1. OBJECTIVES

1.1 Primary

To determine whether denosumab compared to placebo will reduce the rate of first (on-study) clinical fracture (ie, clinically evident fracture with associated symptoms) in women with non-metastatic breast cancer receiving non-steroidal aromatase inhibitor therapy (AIT).

1.2 Secondary

To assess the effect of denosumab compared to placebo on:

Fracture-related secondary endpoints:

- Bone mineral density (BMD) at lumbar spine, total hip and femoral neck in a subgroup of subjects at pre-selected sites
- Incidence of new vertebral fractures (both clinical and morphometric [ie, a fracture in the vertebral column that is not clinically evident and that is asymptomatic])
- Incidence of new or worsening of pre-existing vertebral fractures (both clinical and morphometric)

Disease outcome-related secondary endpoints:

- Disease-free survival (DFS)
- Bone metastasis-free survival (BMFS)
- Overall survival (OS)

To assess the safety and tolerability of denosumab in this population.

1.3 Exploratory

[redacted]

2. BACKGROUND AND RATIONALE

2.1 Disease

Breast cancer is a common malignancy in women, with an incidence rate of over 210,000 cases per year and prevalence rate in excess of 2 million in the US alone (Jemal et al, 2003). Endocrine therapy is recommended for nearly all women with breast cancer that expresses estrogen receptor (ER) or progesterone receptor (PgR) (ER+ or

ER-/PgR+). Aromatase inhibitor therapy inhibits peripheral estrogen synthesis (Thijssen and Blankenstein, 1989; Lake and Hudis 2002). Treatment of advanced ER+ or ER-/PgR+ breast cancer with aromatase inhibitors demonstrated improvements in the objective response rate and time to progression (Dombernowsky et al, 1998; Nabholtz et al, 2000; Mouridsen et al, 2001). Treatment with aromatase inhibitors in the adjuvant setting for postmenopausal women with ER+ or ER-/PgR+ tumors has demonstrated improvements in OS, progression-free survival and incidence of breast cancer in the contralateral breast for women with ER+ or ER-/PgR+ breast cancer (Goss et al, 2003).

Despite these improvements, there is growing awareness of risk of bone loss induced by adjuvant treatment with aromatase inhibitors in postmenopausal women with early stage breast cancer that are ER+ or ER-/PgR+ positive (ATAC trialists group, 2005; Jakesz et al, 2005; BIG 1-98 Collaborative Group, 2005).

An analysis of Arimidex, Tamoxifen Alone or in Combination (ATAC) data showed an increase in the incidence of symptomatic (clinical) fractures (both vertebral and non vertebral), not related to disease progression for the women treated with anastrozole, an aromatase inhibitor, as compared to tamoxifen. Similarly, the Breast International Group (BIG) 1-98 Collaborative group demonstrated that fractures were significantly more frequent in the letrozole group than in the tamoxifen group (5.7% vs. 4.0%, P< 0.001). Derivation of the data suggested an occurrence of approximately 20 fractures per 1000 subject-years (letrozole group).

2.2 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 (RANK/L) system has been identified as an essential mediator of osteoclast formation, function, and survival (Teitelbaum et al, 2003). RANK/L binds RANK on osteoclasts or osteoclast precursors to stimulate or promote differentiation into osteoclasts and activate mature osteoclasts to resorb bone. Therefore, RANK/L is a therapeutic target for diseases associated with increased bone resorption.

Denosumab is a fully human monoclonal IgG2 antibody to RANK/L that binds with high affinity (Kd 3 x 10^{-12} M) and specificity to the soluble and cell membrane-bound forms of human RANK/L. Denosumab is highly specific because it binds only to RANK/L and not to other members of the TNF family, including TNFα, TNFβ, TNF-related

apoptosis-inducing ligand, or CD40 ligand (Elliott et al, 2006). Denosumab binding prevents the activation of RANK and inhibits the formation, activation, and survival of osteoclasts. As a consequence, bone resorption and cancer-induced bone destruction are reduced.

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

2.3 Rationale

In the ATAC study after 5 years of follow-up, despite an improved DFS, a retrospective analysis showed an increase in the incidence of clinical fractures (vertebral and non vertebral not related to disease progression) for the women treated with anastrozole, an aromatase inhibitor, as compared to those treated with tamoxifen, a non-steroidal anti-estrogen that has partial-estrogen-agonist activity (ATAC trialists group, 2005). For the anastrozole treated group, fracture rates were 22.6 per 1000 women-years and 15.6 per 1000 women-years for the tamoxifen treated group (hazard ratio 1.44, 95% C.I. 1.21-1.68, $p < 0.001$).

Estrogen stimulates the osteoblast to produce osteoprotegerin and inhibits the production of RANK/L. In the absence of estrogen, the reduced levels of osteoprotegerin result in increased bone resorption due to unopposed actions of RANK/L. Denosumab inhibits RANK/L, resulting in the inhibition of bone resorption.

To date, there are no approved treatments to prevent bone loss in this at-risk population and no trials have been published using bisphosphonates for the specific treatment or prevention of bone loss that occurs during or after treatment with aromatase inhibitors. Ongoing studies are investigating the role of bisphosphonates for this particular indication. Two large 5-year trials (Z-Fast in the US and ZO-FAST in Europe) are investigating immediate and delayed treatment with zoledronic acid (4 mg via 15-minute infusion every 6 months) in more than 1500 post-menopausal women receiving adjuvant therapy with the aromatase inhibitor letrozole for early stage hormone receptor positive breast cancer (Brufsky et al, 2004). The primary end-point in this trial is lumbar BMD at 12 months.

As the use of AIT becomes more prevalent, it will become increasingly important to identify effective treatments to prevent and treat bone loss in women who are undergoing adjuvant treatment with aromatase inhibitors. For the oncology clinical

community it will be important to establish which treatments will be effective in reducing clinical fractures as described in the ATAC study.

Because of its profile as a fast-acting, potentially reversible and potent inhibitor of osteoclastic bone resorption, denosumab may be an effective and convenient therapy for osteoporosis associated with hormone ablation therapy, including AIT. If successful, this study will show that denosumab reduces the rate of clinical fracture in the population of subjects on AIT.

The pivotal 20030216 – trial (denosumab versus placebo in the treatment of women with postmenopausal osteoporosis) showed a clinical fracture reduction by 30% by denosumab compared to placebo. Based upon the review of these fracture data in the 20030216 trial (Cummings et al, 2009) and taking into account that aromatase inhibition increases bone turnover (Eastell et al, 2006), a hazard ratio was calculated for the 20050209 – trial and a fracture risk reduction of 30% by denosumab compared to placebo (or hazard ratio = 0.70) is more likely to reflect the clinical fracture risk for this postmenopausal adjuvant breast cancer population treated with aromatase inhibition.

The Austrian Breast and Colorectal Cancer Study Group (ABCSG) 18 primary analysis showed that adjuvant denosumab 60 mg, administered twice yearly, reduces the risk of clinical fractures, including new vertebral fractures and new or worsening vertebral fractures, in postmenopausal women with breast cancer who are receiving AIT and also increases BMD at the lumbar spine, total hip, and femoral neck. There were no new safety findings in the study and the safety profile was similar to that previously observed with Prolia®.

Subcutaneous denosumab 60 mg every 6 months significantly delayed the time to first clinical fracture (HR = 0.50, 95% confidence interval [CI] 0.39-0.65, p <0.001). This reduction in fractures between denosumab and placebo arms (overall 92 vs 176, respectively) was similar in all subject subgroups, including subjects with normal bone health at baseline (T-score ≥ -1, n = 1872, HR = 0.44, 95% CI 0.31-0.64, p < 0.001) and osteopenic subjects (T-score < -1, n = 1548, HR = 0.57, 95% CI 0.40-0.82, p = 0.002). Denosumab also significantly increased BMD of lumbar spine (10.02%), total hip (7.92%), and femoral neck (6.51%) at 36 months compared with the placebo group (all adjusted p-values < 0.001). Denosumab treatment also significantly reduced the incidence of new vertebral fractures at 36 months, with 27 fractures in 835 patients in the denosumab group compared with 49 fractures in 809 patients in the placebo group (odds ratio 0.53 [95% CI 0.33 -0.85], p-value = 0.009) and the incidence of new or

worsening vertebral fractures at 36 months (31 of 835 patients in the denosumab group compared with 55 of 809 patients in the placebo group; odds ratio 0.54 [95% CI 0.34-0.84], p = 0.007). There were no differences between the denosumab and placebo groups with respect to subject incidence of adverse events (1366 [80%] vs 1334 [79%]), or serious adverse events (SAEs) (521 vs 511; 30% in each group). Despite proactive adjudication of every potential osteonecrosis of the jaw (ONJ) by an international expert panel, no ONJ case was observed. No atypical femoral fractures were identified.

For these postmenopausal breast cancer patients with modest risk of disease recurrence, effectively preventing the most serious side effect of their aromatase inhibitor treatment is highly beneficial (Gnant et al.; Lancet 2015).

Based on the results of the ABCSG 18 primary analysis, the Data Monitoring Committee (DMC) recommended offering denosumab 60 mg for up to 36 months (maximum of 7 doses) to subjects, who after unblinding, were shown to be in the placebo arm.

2.4 Hypotheses

2.4.1 Clinical Efficacy Hypothesis

Denosumab, when administered SC at a dose of 60 mg every 6 months, will be considered efficacious in breast cancer subjects receiving AIT if the rate of first clinical fractures (vertebral and non-vertebral – consistent with ATAC) in denosumab-treated subjects is lower than that in placebo-treated subjects. It is anticipated that denosumab will reduce the rate by 30% compared with placebo (ie, the true hazard ratio of denosumab compared with placebo is 0.70).

2.5 Clinical Safety Hypothesis

Denosumab, when administered SC at a dose of 60 mg every 6 months will be well tolerated in breast cancer subjects receiving AIT.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multi-center phase 3, randomized, double-blind, placebo-controlled study to determine the treatment effect of denosumab in subjects with breast cancer treated with an approved non-steroidal aromatase inhibitor, eg, anastrozole. Approximately 3400 subjects will be randomized in a 1:1 ratio to receive either denosumab administered at a dose of 60 mg or placebo SC every 6 months (Q6M) in a blinded manner. Subjects will be recruited over approximately 82 months. The randomization

schedule will be stratified by: type of hospital (major academic centers or other centers), prior AI usage (Y/N) and total lumbar spine BMD score at baseline (T-score < -1.0 vs ≥ -1.0).

Subjects will remain on investigational product (IP) until the required number of events (where an event is defined as first clinical fracture) is reached and all subjects had the opportunity to receive a minimum of at least 2 doses of IP, whichever occurs later. The primary analysis data cut-off date (PADCD) is defined as the time at which the required number of events is reached and all subjects have had the opportunity to receive at least 2 doses of IP. When the PADCD is reached, all subjects will discontinue IP.

For all subjects whose last regular study visit within 6 months (+ 45 days time window) prior to the PADCD was a yearly visit (eg, month 12, 24, etc) and radiological assessments were performed, this visit will be considered an EOT visit (corresponding case report form [CRF] will have to be completed). For those subjects, the next visit will be regarded as long-term follow-up (LTFU) visit, at which an antibody sample will be taken. Those subjects, for whom the radiological assessments were not performed, will need to attend the next scheduled 6 months visit, when radiological assessments (vertebral x-rays, dual X-ray absorptiometry [DXA]) will take place and an antibody sample will be taken. For these subjects this visit will be considered as EOT visit.

All subjects, whose last regular study visit within 6 months (+ 45 days time window) prior to the PADCD was a 6 months visit (eg, month 6, 18, etc), will have to attend the next regularly scheduled yearly study visit (eg, month 12) within 6 months after PADCD at the latest and perform all corresponding assessments, including antibody sampling.

Data on fractures occurring between the last visit prior to PADCD and PADCD have to be collected via telephone or physical visits within six months after PADCD at the latest.

Subjects who withdraw from IP prior to the observed PADCD will continue to attend Q6M study visits for assessment of the primary and secondary end-point and safety.

Subjects completing or discontinuing AIT will have the opportunity to remain on IP for at least 2 doses of IP after their last scheduled study visit during which they were still on AIT. Following the study PADCD, subjects will be followed for DFS, BMFS, and OS every 12 months (Q12M) by clinic visits or telephone contacts starting from their last study visit (considered as EOT visit) until a maximum of either 18 or 66 months after the PADCD, depending on an interim analysis at PADCD (see Sections 7.16 and 10.5). Based on the DMC recommendation that interim futility analysis of DFS did not indicate

futility, it was decided to follow subjects until a maximum of approximately 66 months after PADCD. Following regulatory and Institutional Review Board / Independent Ethics Committee (IRB/IEC) approval of Protocol Amendment 4, further data will be assessed.

Open-label Phase

Due to the statistically significant differences in the primary endpoint and fracture-related secondary endpoints between the denosumab arm and the placebo arm demonstrated at the primary analysis (Gnant et al.; Lancet 2015), willing and eligible subjects randomized to placebo during the double-blind phase may participate in an open-label phase (OLP) and receive denosumab 60 mg Q6M for up to 36 months (maximum of 7 doses), as recommended by the DMC.

After regulatory and IRB/IEC approval of Amendment 4, the opportunity to start open-label denosumab will open for a 12-month period. Subjects who consent and fulfil the eligibility criteria will receive denosumab in the OLP for up to 36 months (a maximum of 7 doses). Subjects who do not fulfil the eligibility criteria or do not consent will complete LTFU assessments only (Appendix A).

Subjects who do not receive open-label denosumab will be followed once a year (Q12M study visit) by clinic visits or telephone contacts for:

- DFS, BMFS, and OS
- Clinical fracture recording (including SAE reporting of suspected atypical femoral fracture cases)
- Concomitant bone affecting medication
    - Bone targeted therapy (eg, bisphosphonate or denosumab)
    - Glucocorticoids
    - Antiepileptic drugs
    - Antidepressants
    - Insulin
- Anti-cancer related therapy (eg, chemotherapy or endocrine therapy)
- Supplements (vitamin D and calcium)

Subjects who receive open-label denosumab will attend clinic visits Q6M for:

- Administration of denosumab (60 mg SC)
- Collection of serious and non-serious **adverse events** [(S)AEs] of special interest (oral events) and SAEs
- Clinical fracture recording (including SAE reporting of suspected atypical femoral fracture cases) (Q12M only)

- DFS, BMFS, and OS (Q12M only)
- Concomitant bone affecting medication (Q12M only)
  - Bone targeted therapy (eg, bisphosphonate or denosumab)
  - Glucocorticoids
  - Antiepileptic drugs
  - Antidepressants
  - Insulin
- Anti-cancer related therapy (eg, chemotherapy or endocrine therapy) (Q12M only)
- Supplements (vitamin D and calcium) (Q12M only)

In addition, for all subjects, BMD data will be collected at any time a DXA scan is performed for BMD analysis as standard of care from PADCD to end of study (EOS), these data will be collected in the CRF.

Zoledronic Acid (ZA) Substudy:

A substudy has been added in Appendix G to evaluate subjects completing open-label denosumab treatment, to either receive a single dose of ZA, or to be managed according to current standard of care (SOC) for the patient population.

Subjects enrolled in the main study who received denosumab during the open label phase and are deemed eligible per the inclusion and exclusion criteria, may choose to participate in this substudy. Subjects that are not included in the substudy will end study as planned. Protocol-defined denosumab administration will complete at end of the open-label period no matter if subjects participate in the substudy or not.

Subjects enrolled in the substudy will be randomized to either receive a single dose of ZA (Therapy Arm) or will be managed according to the current SOC for this patient population (Control Arm). Day 1 for both arms is 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit. Follow up will continue for a total of 18 months after day 1.

In the event an adverse event of special interest (**renal toxicity, clinically relevant hyper/hypocalcemia and** oral event) or other SAE is identified outside the subjects' scheduled visits, the standard guidance in Section 9 should be followed.

It is highly recommended that all subjects should receive daily supplements of at least 500 mg elemental calcium and at least 400 I.U. vitamin D.

Double-blinded Phase

For a subject with > 10% loss of BMD at the total hip or lumbar spine over any 1-year period, an informed discussion will take place between the investigator and the subject regarding alternative therapies and appropriate treatment. If the selected treatment option does not include commercially available denosumab (ie, XGEVA® or Prolia®), IV bisphosphonates or orally administered bisphosphonate therapy lasting longer than 30 days, which is exclusionary (leading to early EOT), the subject will remain in the study.

The number of primary endpoint events observed will drive the timing of the primary and final analyses (refer to Section 10.5 for details). The actual timing of the primary analysis will depend on the rate of recruitment into the study and the rate at which clinical fractures are observed.

A study schema at the end of the protocol synopsis section describes the overall **main** study design.

The study endpoints are defined in Section 10.2.

3.2 Number of Centers

ABCSG will conduct the study. A network of approximately 60 to 80 centers is anticipated to participate. Sites that do not enroll subjects within 6 months of site initiation may be closed.

3.3 Number of Subjects

Participants enrolled in this clinical investigation shall be referred to as “subjects”. Approximately 3400 subjects will be enrolled into the study. Eligible subjects will be randomized to 1 of the 2 treatment groups.

Based on experience of dropout rates in previous studies it is anticipated that approximately 22% of patients over 3 years are expected to discontinue treatment. However, due to the nature of standard medical practice it is anticipated that even when subjects discontinue treatment, almost 100% of them will be followed up within the study for the occurrence of the primary end-point. Refer to Section 10.3 for details on the rationale for the number of subjects.

3.4 Estimated Study Duration

The actual timing of analyses will be determined by the PADCD. Study duration is estimated to be 169 months, which includes an enrollment period of approximately 82 months, an end of the treatment phase (ie, the PADCD) of approximately 21 months and approximately 66 months following the PADCD for a 5 year long-term follow-up including an OLP (12 months unblinding option and a maximum of 36 months of treatment) (see Sections 7.16 and 10.5).

3.4.1 Study Duration for Participants

Study duration for individual subjects will vary depending on the PADCD. Based on the estimated recruitment period and expected occurrence of clinical fractures, the last subject randomized will participate in the treatment phase until they have had the opportunity to receive at least 2 doses of IP before the study treatment phase ends. Following the study PADCD, subjects will be followed-up Q12M by clinic visits or telephone contacts starting from their last study visit (considered as EOT visit) for a maximum of approximately 66 months after the PADCD.

Subjects who receive open-label denosumab will be followed-up until completion of 36 months of treatment or approximately 66 months after PADCD, whichever is longer. The expected time on study is up to approximately **169** months.

3.4.2 End of Treatment

The End of Treatment is defined for each subject as the point in time when the last dose of blinded investigational product is administered.

3.4.3 Long-term Follow-up

Subjects will be followed for DFS, BMFS, and OS Q12M by clinic visits or telephone contacts starting from their last study visit (considered as **EOT** visit) for approximately 66 months after the PADCD (see Sections 7.16 and 10.5). Following regulatory and IRB/IEC approval of Protocol Amendment 4, further data will be assessed (see Section 3.1).

Subjects who do not receive open-label denosumab will be followed for DFS, BMFS, and OS once a year (Q12M study visit) by clinic visits or telephone contacts until approximately 66 months after PADCD. Additionally, further data will be assessed (see Section 3.1).

Subjects who receive open-label denosumab will have Q6M on-site visits for administration of denosumab (60 mg SC Q6M) and monitoring of SAEs and (S)AEs of

special interest and will be followed Q12M for DFS, BMFS, and OS until either approximately 66 months after PADCD or completion of treatment, whichever is longer. Additionally, further data will be assessed (see Section 3.1).

3.4.4 End of Open-label Treatment

The end of open-label treatment is defined for each subject as the point in time the last dose of denosumab is administered.

3.4.5 End of Study (Double-blind Phase and End of ZA Substudy)

The end of the study will occur when the last subject has completed their last formal visit or last formal contact or an unscheduled study visit in case of early withdrawal from the study. This is expected to occur when the last subject completes the **ZA substudy**. End of study reasons include 3 early EOS reasons (death, lost to follow-up, consent withdrawal) and per protocol EOS.

At End of Study, the end of study CRF has to be completed for each subject.

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 (age), date, and outcome of the screening process (eg, enrolled into study, reason for ineligibility, or refused to participate).

4.1 Inclusion Criteria for Double-blind Phase

4.1.1 Histologically or cytologically confirmed adenocarcinoma of the breast

4.1.2 Female subjects with non-metastatic disease who are ER and/or PgR positive, and who have completed their treatment pathway (surgery, chemotherapy)

4.1.3 Subjects who are currently on, or will initiate an approved non-steroidal aromatase inhibitor therapy (eg, anastrazole) in the adjuvant setting

4.1.4 Postmenopausal woman[1,2], defined as a woman fulfilling any one of the following criteria:

- Having undergone a bilateral oophorectomy;
- Age ≥ 60 years;
- Aged < 60 years meeting the following requirements:

[1] For subjects previously treated with a luteinizing hormone-releasing hormone antagonist, the last dose must have been 4 months prior to randomization, and FSH and estradiol must be in the postmenopausal range.

[2] Subjects who have received adjuvant or neoadjuvant chemotherapy must have met 1 of the above criteria for postmenopausal status prior to that chemotherapy.

- Follicle-stimulating hormone (FSH) and estradiol in the postmenopausal range;
- A negative pregnancy test within 7 days prior to randomization. Subjects who have undergone a hysterectomy do not require a pregnancy test.

4.1.5 Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 (see Appendix E)

4.1.6 Before any study-specific procedure is performed, a signed and dated written informed consent must be obtained (see Section 12.1)

4.2 Exclusion Criteria for Double-blind Phase

4.2.1 Aromatase inhibitor therapy for more than 24 months

4.2.2 Prior or concurrent treatment with Selective Estrogen Receptor Modulators (SERMs) (eg, tamoxifen)

4.2.3 Evidence of metastatic disease

4.2.4 Current or prior IV bisphosphonate administration

4.2.5 Oral bisphosphonate treatment:

- Greater than or equal to 3 years continuously
- Greater than 3 months but less than 3 years unless subject has had a washout period of at least 1 year prior to randomization
- Any use during the 3-month period prior to randomization

4.2.6 Prior administration of denosumab (AMG 162)

4.2.7 Known liver or renal disease as determined by the investigator and indicated by the following criteria:

- **Aspartate** aminotransferase ≥ 2.5 x upper limit of normal (ULN)
- Alanine transaminase ≥ 2.5 x ULN
- Serum creatinine ≥ 2 x ULN

4.2.8 Recurrence of the primary malignancy (eg, during the allowed interval of pretreatment with AI)

4.2.9 Diagnosis of any second non-breast malignancy within the last 5 years, except for adequately treated basal cell or squamous cell skin cancer, or for in situ carcinoma of the cervix uteri

4.2.10 Known history of any of the following conditions either by subject self report or chart review

- Paget's disease (bone), Cushing's disease, hyperprolactinemia or other active metabolic bone disease
- Hypercalcemia or hypocalcemia: as defined by calcium outside the normal range (A single value outside the normal range does not necessarily constitute hypercalcemia or hypocalcemia, but should be 'corrected' before including the subject. Subjects with a known history of hypercalcemia or hypocalcemia cannot be included)

- Major surgery, or significant traumatic injury occurring within 4 weeks prior to randomization
- Known human immunodeficiency virus infection
- Active infection with hepatitis B or hepatitis C virus

4.2.11 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

4.2.12 Thirty days or less since receiving an investigational product or device in another clinical study

4.2.13 Known sensitivity to any of the products to be administered during the study (eg, mammalian derived products, calcium or vitamin D)

4.2.14 Subjects who are pregnant, breastfeeding, or plan to become pregnant during the course of the study. All subjects with reproductive potential must have a negative pregnancy test within 7 days before randomization

4.2.15 Any kind of disorder that compromises the ability to give written informed consent and/or comply with study procedures

4.3 Inclusion Criteria to Receive Open-label Phase Denosumab

4.3.1 Obtain signed and dated written informed consent prior to performing any study-specific procedure (see Section 12.1)

4.3.2 Subjects currently taking an approved non-steroidal AIT (eg, anastrazole) or who have completed or discontinued AIT within 12 months prior to participation in the OLP

4.3.3 Randomized to placebo arm during the double-blind phase (as determined by unblinding procedures)

4.4 Exclusion Criteria to Receive Open-label Phase Denosumab

4.4.1 Current or prior IV bisphosphonate administration

4.4.2 Subjects meeting the following criteria for oral bisphosphonate treatment:

- Greater than or equal to 3 years continuously
- Greater than 3 months but less than 3 years unless subject has had a washout period of at least 1 year prior to participation in the OLP
- Any use during the 3-month period prior to participation in the OLP

4.4.3 Prior or concurrent treatment with SERMs (eg, tamoxifen)

4.4.4 Subjects who ended treatment with investigational product (IP) prematurely in the double-blind phase

4.4.5 Treatment with commercial denosumab (Prolia® or Xgeva®) prior to participation in the OLP

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, ABCSG and Amgen require a copy of the written Independent Ethics Committee (IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 12.3). All subjects or legally acceptable representatives must personally sign and date the consent form before enrollment.

The enrollment date is defined as the date the subject is randomized (ie, the date the site calls the interactive voice response system (IVRS) to complete the randomization process).

5.1 Screening

All subjects who enter into the screening period for the study (defined as the point at which the subject signs the informed consent) will receive a unique 9-digit subject identification number before any study procedures are performed. The subject identification number will be provided by the IVRS. This number 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, enrollment, or randomization. This number will not necessarily be the same as the randomization number assigned for the study.

The subject identification number will consist of 9 digits. The first 3 digits will represent a protocol identifier (ie, 018) and will be identical for all sites. The next 3 digits will represent the site number (eg, 001, 002, 003) and will be identical for all subjects at a particular site. The last 3 digits will represent the subject identification and will be assigned in sequential order, per site, as subjects are screened (eg, 001, 002, 003). Therefore, the first subject to enter screening at site 001 will receive the number [redacted]; the second subject at this site will receive the number [redacted], etc. This number will not be the same as the randomization number assigned for the study.

Refer to Section 7 and Appendix A for screening procedures and medical history details. Subjects may be re-screened 1 time. If a subject fails to meet all entry criteria after 2 attempts, the subject will not be enrolled into the study.

5.2 Treatment Assignment (Blinded Treatment Phase)

A subject who gives written informed consent and who satisfies all the inclusion and exclusion criteria may be randomized into the study. Questions regarding subject

eligibility should be discussed (and documented) with Amgen or the ABCSG project manager before randomization.

A subject will be randomized to receive either denosumab or placebo by calling the IVRS after completion of all screening assessments and meeting all eligibility criteria. Administration of IP must occur within 8 days after randomization.

Once a subject is ready for her initial or on-study scheduled dose, the site personnel will call the IVRS vendor to obtain a box number assignment. The box number will be unique to each subject and must be recorded in the CRF and in the accountability records. Please refer to specific instructions provided by the IVRS vendor for additional information.

5.3 Randomization

A subject will be assigned by an IVRS to 1 of 2 treatment groups (denosumab or placebo), in a 1:1 ratio, with the assignment balanced with respect to stratification factors at the time of study entry. The randomization schedule will use randomly permuted blocks, and will be stratified by type of hospital (major academic centers or other centers), prior AI usage (Yes or No) and total lumbar spine BMD score at baseline (T-score < -1.0 or ≥ -1.0). A subject will be considered randomized once a randomization number is assigned. A subject may only be randomized once and each randomization number may only be assigned to 1 subject. The randomization list will be generated and maintained by an Amgen representative not involved in the conduct of the study.

The randomized assignment for investigational product will remain blinded to the subject, center personnel, and all Amgen/ABCSG study personnel and designees involved with the conduct of the study, with the exception of those circumstances where the investigator deems it necessary to break the blind in order to provide appropriate medical treatment for the subject. Refer to Section 10.4 for details on when and how the randomization code may be broken.

5.4 Open-label Phase

The opportunity to start open-label denosumab will be open for 12 months following Protocol Amendment 4 regulatory and IRB/IEC approval.

After signing of the ICF, unblinding of subjects considered eligible for treatment with denosumab can occur. The first dose of denosumab must be administered within 8 days of unblinding.

5.5 Unblinding Procedures

Unblinding of willing subjects thought to be eligible to receive denosumab in the OLP will be done by authorized site personnel using the unblinding (code break) call with the IVRS call center.

6. TREATMENT PROCEDURES

Denosumab and placebo will be considered the only investigational products in this study. It is highly recommended that all subjects receive daily calcium and vitamin D. These medications will be referred to as supplements.

6.1 Blinded Treatment Phase

6.1.1 Investigational Product Dosage, Administration, and Schedule

Subjects will be randomized 1:1 to receive 60 mg of denosumab or placebo every 6 months. Subjects will remain on study treatment until the required number of events is reached and until they have had the opportunity to receive a minimum of at least 2 doses of IP, whichever occurs later. Denosumab and placebo will be administered as a SC injection.

All doses should be administered by a licensed health care professional after all other study visit procedures have been completed. The first dose of investigational product must be administered within 8 days after randomization.

There have been no reports of overdose with this product. It is possible that an overdose may result in hypocalcemia. Hypocalcemia, if severe, should be managed by oral or parental calcium replacement, as clinically indicated.

Refer to the pharmacy guide (Appendix C) for detailed information on the administration of denosumab.

6.1.2 Missed Dose

If a subject misses a scheduled SC injection, then they should return to the clinic as soon as possible for investigational product administration (preferably no later than 45 days after their scheduled dose). If more than 45 days have elapsed since the scheduled IP dose, the IP dose will be considered a missed dose. The next dose is to be given on the next scheduled visit date (based on study day 1).

6.1.3 Dose Escalation and Stopping Rules

There are no planned dose escalations in this study.

Administration of investigational product will be withheld for any subject who experiences a grade 3 or 4 adverse event (refer to Common Terminology Criteria for Adverse Events [CTCAE] Version 3.0; see Appendix B for link) reported by the investigator to be related to investigational product. Re-exposure to investigational product may occur only when the event resolves to grade 1 or better and if the investigator and sponsor agree subject safety will not be compromised.

Subjects will continue to receive investigational product until one of the following occurs: the PADCD date is reached (see Glossary), the investigator or Amgen recommends discontinuation, the subject decides to discontinue for any reason, or the subject develops metastases. For a detailed list of EOT reasons see Section 8. A Schema in the protocol synopsis describes the dosing schedule.

6.1.4 Dosage Adjustments

There will be no dose adjustments of the investigational product in this study.

6.1.5 Supplements

It is highly recommended that all subjects receive daily supplements of at least 500 mg of elemental calcium and at least 400 IU vitamin D throughout investigational product administration. Calcium and vitamin D dosages may vary due to differences in availability. (Calcitriol is not allowed – see Section 6.1.7).

Supplements will be recorded on a CRF.

6.1.6 Concomitant Therapy

6.1.6.1 Blinded Treatment Phase 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 6.1.7. All concomitant medications, including over-the-counter products, administered from enrolment through 30 days after the last dose of investigational product, must be recorded in the CRF. In addition, the dose administered will be recorded in the CRF for vitamin D supplements, calcium supplements, and aromatase inhibitor therapy.

6.1.6.2 Open-label Concomitant Therapy/ Long-term Follow up

Throughout the OLP, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.2.5. Concomitant therapies being taken for the disease under study (eg, chemotherapy, endocrine therapy) and bone affecting medication

(eg, bisphosphonates, glucocorticoids, antiepileptic drugs, antidepressants, and insulin) will be recorded in the CRF through the end of the study for all subjects.

In addition, confirmation of whether a subject is taking calcium and vitamin D supplements will be recorded in the CRF.

6.1.7 Prohibited Therapy During Blinded Phase

Bisphosphonates (IV or over 30 days oral) or commercially available denosumab (ie, XGEVA® or Prolia®) are not to be administered during the treatment phase. Subjects who begin a bisphosphonate regimen (IV or over 30 days oral) or commercially available denosumab during the treatment phase will be withdrawn from investigational product (early EOT).

The following medications should not be administered during the treatment phase: fluoride (for osteoporosis), strontium ranelate, systemic estrogen, selective estrogen receptor modulators (eg, raloxifene), tibolone, calcitonin, anabolic steroids, parathyroid hormone (or a derivative), calcitriol, tamoxifen and any other medication that is known or suspected to have activity on bone metabolism (except calcium and vitamin D).

Use of any other investigational product is not permitted until PADCD.

6.2 Open-label Phase

Willing and eligible subjects will receive denosumab 60 mg Q6M SC for up to 36 months (maximum of 7 doses).

Subjects will remain on denosumab 60 mg Q6M until they complete 36 months (7 doses) of treatment, the investigator or Amgen recommends discontinuation, or the subject decides to discontinue for any reason (see Section 8.1). See also Denosumab Dosage, Administration, and Schedule.

All doses should be administered by a licensed health care professional.

There have been no reports of overdose with this product. It is possible that an overdose may result in hypocalcemia. Hypocalcemia, if severe, should be managed by oral or parenteral calcium replacement, as clinically indicated.

Refer to the pharmacy guide (Appendix C) for detailed information on the administration of denosumab.

6.2.1 Missed Dose During OLP

Please see Section 6.1.2 for guidance on missed doses.

6.2.2 Dose Escalation and Stopping Rules

Please see Section 6.1.3 for guidance on dose escalation and stopping rules.

6.2.3 Dosage Adjustments

There will be no dose adjustments of denosumab.

6.2.4 Supplements

Please see Section 6.1.5.

6.2.5 Prohibited Therapy During Open-label Phase

For subjects receiving denosumab in the OLP, bisphosphonates (IV or over 30 days oral) are not to be administered during the treatment phase. Subjects who begin a bisphosphonate regimen (IV or over 30 days oral) during the treatment phase will be withdrawn from denosumab.

For additional information, refer to the PROLIA® prescribing information.

7. STUDY PROCEDURES

Study assessments will be performed only after written informed consent is obtained. The schedule of assessments is provided in Appendix A.

7.1 Screening Visit

With the following exceptions, all screening procedures must be completed ≤ 35 days before the day of randomization.

For eligibility purposes, all subjects must have a bone scan that has been performed within 6 months of randomization.

DXA and X-rays should ideally be performed within the 35 day screening window. However, if necessary, DXA and/or X-ray assessments must have been performed within 120 days of randomization.

7.2 Study Day 1

Enrollment date is defined as the date of randomization. Study day 1 is defined as the day that the initial dose of investigational product is administered to the subject. The initial dose of investigational product will be administered within 8 days after randomization.

7.3 Treatment Phase Visits

Treatment phase visits will occur every 6 months (± 45 days) from study day 1.

If a subject's visit is delayed, their subsequent visit date should not be shifted, but revert back to the original schedule.

7.4 Medical History

The subject's medical history will be obtained prior to enrollment and recorded on the CRF. Detailed history of the subject's breast cancer will be obtained.

7.5 Medication History

Information on all medications, surgical procedures, and radiotherapy, including intra-operative radiotherapy, specifically used to treat the subject's cancer prior to study day 1 will be recorded on the CRF.

In addition, information on all known previous bisphosphonate use will be recorded on the CRF.

7.6 Physical Examination

Each physical examination visit will include assessment of ECOG performance status, height (during screening only), weight, and vital signs (temperature, pulse, and blood pressure). Refer to Appendix E for ECOG performance status criteria. Results from a physical examination performed as standard of care within the 30-day period prior to signing the ICF may be used as screening data for this study.

7.7 Clinical Fracture Assessment

At each study visit the investigator will assess if the subject has any relevant symptoms of clinical fractures. If new symptoms are reported, the investigator will use clinical judgment to determine if these symptoms warrant further investigation and whether a diagnostic x-ray should be performed. All clinical fractures, except those of the skull, face, fingers, and toes, which are typically not associated with osteoporosis, will be included in the analysis of clinical fractures.

A qualified member of the study site will contact the subject via telephone approximately every 12 weeks after the study visit to check if there have been any clinical fractures in order to aid event tracking. These telephone contacts will begin at a timepoint closer to the required number of events that define the end of the study. In case a clinical fracture is reported, the patient should attend an unscheduled visit.

The CRF will capture subject reports of pain and/or other symptoms indicative of fracture or deterioration of mobility. The investigator will be asked to confirm if in his/her opinion the symptom locality is linked to the fracture.

The Blinded Review Committee will review radiographs and reports of those subjects for whom the local investigator cannot easily confirm a clinical fracture and for cases where the link between symptom locality and fracture is ambiguous. Details of the processes followed by the Blinded Review Committee will be included in a separate charter.

If the subject reports symptoms between study visits that would suggest a clinical fracture then the same procedures as described above should be followed.

A copy of any radiographs or radiologist reports must be included in the subject's study records. For the purpose of the study, all clinical fractures must be confirmed by x-ray.

7.7.1 Assessment of Clinical Fractures During Open-label Phase

Clinical fractures identified by the site will be recorded on the CRF for all subjects.

7.8 Lateral Spine X-ray

X-rays of the lateral thoracic and lumbar spine will be acquired according to separate instructions per the schedule outlined in Appendix A. Sites will be pre-qualified to conduct these x-rays based on pre-defined criteria. Any site that does not meet the pre-qualification criteria will send their subjects to the nearest qualified center for on-study vertebral x-rays. Assessment of vertebral fractures will be performed by an expert radiologist at the central imaging center using a semiquantitative grading scale (Genant et al, 1993): Grade 1, 20% to 25% reduction in vertebral height (anterior, middle, or posterior); Grade 2, 25% to 40% reduction in height; Grade 3, greater than 40% reduction in height.

Prevalent vertebral fractures will be assessed and recorded at baseline. For assessment of incident vertebral fracture, x-rays will be reviewed blinded to treatment but not to sequence. The semiquantitative scale will be used. For the study a new vertebral fracture is defined as a fracture in a previously undeformed vertebrae. Vertebral fractures will include new compression fractures, defined as those compression fractures having a decrease in total anterior or posterior height of at least 25% from baseline. New vertebral fractures will be classified as either clinical or morphometric depending on whether or not in the investigator's opinion the symptom locality can be linked to the fracture. Worsening of pre-existing fractures will also be assessed. Worsening is defined as an increase in fracture severity of at least 1 grade on the semiquantitative scale.

If a subject has acute back pain at a time point other than when a scheduled spinal x-ray is obtained, and occurrence of a vertebral fracture is suspected, the investigator should

obtain a lateral spinal x-ray to confirm the presence of clinical fracture as described in Section 7.7. A copy of any radiographs or radiologist reports must be included in the subject's study records.

7.9 Dual Energy X-ray Absorptiometry (DXA) Assessment

All subjects will be required to undergo bone densitometry assessments of the lumbar spine and proximal femur performed by DXA per the schedule outlined in Appendix A.

The same DXA machine must be used for all study procedures for a particular subject. The left side should be used for the proximal femur scans, unless prohibited, eg, hip implant.

Lumbar spine scans must include L1 through L4. Vertebrae that are unevaluable (eg, clearly fractured, ossification) will be excluded from the lumbar spine DXA analysis.

Detailed instructions for scan acquisition will be in a separate manual.

7.9.1 Screening DXA

Densitometry measurements of both the lumbar spine and the proximal femur must be performed at screening. The lumbar spine DXA should be analyzed by the local DXA technician to determine the stratification factor based on the subject's lumbar T-score. At baseline, at least 2 lumbar vertebrae should be evaluable.

7.9.2 On-Study DXA

All on-study bone densitometry assessments will be measured at the lumbar spine and proximal femur.

For a subject with > 10% loss of BMD at the total hip or lumbar spine over any 1-year period, an informed discussion will take place between the investigator and the subject regarding alternative therapies and appropriate treatment. If the selected treatment option does not include commercially available denosumab (ie, XGEVA® or Prolia®) or bisphosphonates, which is exclusionary, the subject will remain in the study. Those subjects for whom IV treatment with bisphosphonates or orally administered bisphosphonate therapy lasting longer than 30 days will be considered the best option will be removed from IP treatment.

The analysis for the secondary objective (percent change in lumbar spine, total hip and femoral neck BMD from baseline to months 12, 24, and 36) will only include the data collected from pre-selected sites.

[redacted]

7.10 Bone Scan

A bone scan is required at screening to rule out metastases. If the DXA and bone scan are performed on the same day, then the DXA scan must be performed first. The radioactive nucleotide used in the bone scan can interfere with the BMD measurement. If the bone scan is performed first, then at least 72 hours must elapse before the DXA scan is performed.

7.11 Laboratory Assessments

All on-study blood samples will be processed and sent to the local laboratory with the exception of the denosumab antibody samples.

Specific instruction will be provided on how the denosumab antibody samples should be handled and stored.

7.12 Blood and Serum Assessments

All blood samples will be obtained by venipuncture before investigational product administration. The total volume of blood drawn from a subject throughout the study (based on an average treatment period of 48 months) will be approximately 200 mL, including screening.

Denosumab antibody level will be assessed at screening and the End of Treatment visit during the double-blind phase.

Blood will be obtained for the following assessments at the time points outlined in Appendix A. Table 1 outlines the specific analytes for each assessment.

Table 1. Serum and Blood Sample Analyte Listing

Serum Chemistry	Hematology	Other
Sodium	Red blood cells	Denosumab antibody assay **(only double blind study)**
Potassium	Hemoglobin	
Calcium	Hematocrit	
Blood Urea Nitrogen/Urea	Platelets	
Creatinine	White blood cells	
Total bilirubin		
Alkaline phosphatase		
Alanine transaminase		
Asparate aminotransferase		
LDH		
Gamma GT		
Albumin		

[redacted]

7.13 Adverse Events

Blinded Treatment Phase

Subjects will be evaluated for adverse events at each clinic visit from signing informed consent through 30 days after their last dose of investigational product during the blinded phase. Adverse events will be recorded in the CRF.

Fractures and their associated symptoms will not be reported as adverse events. Clinical fractures and vertebral fractures (morphometric or clinical) will be considered as an end-point and recorded on a specific CRF page. This CRF will also capture subject reports of pain or other symptoms indicative of fracture or deterioration of mobility.

However, if the nature of a fracture or its associated symptoms can be classified as a serious adverse event (see Section 9.1.2), then these should be recorded on a Serious Adverse Event Report form (see Appendix F) and faxed to the local Amgen Safety Specialist within 24 hours of discovery or notification of the event. (See Section 9.3).

Open-label phase / Long-term Follow-up

During the OLP/LTFU, [redacted] will be documented in the CRF only for subjects receiving denosumab.

Clinical fractures will be collected and any suspected atypical femoral fracture (femur midshaft fracture, femur subtrochanteric, femur distal) associated with minimal trauma

will be classified as an SAE for all subjects (see Section 9.1.2), and should be recorded on a Serious Adverse Event Report form (see Appendix F) and faxed to the local Amgen Safety Specialist within 24 hours of discovery or notification of the event (see Section 9.3).

7.14 Early Withdrawal From Treatment

Subjects who discontinue early from treatment will continue to attend the study visits every 6 months (without investigational product administration) until the study PADCD is reached.

At these visits the investigator will assess the subject for clinical fractures as described in Section 7.7. DXA and vertebral x-rays will be performed per the schedule in Appendix A. Important protocol deviations will only be reported through 30 days after the last administration of IP.

Subjects who withdraw from denosumab during the OLP will have follow-up survival data collected every 12 months for up to approximately 66 months after PADCD.

7.15 End of Treatment

Subjects will undergo EOT assessments as described in Appendix A as follows:

For all subjects, whose last regular study visit within 6 months (+ 45 days time window) prior to the PADCD was a yearly visit (eg, month 12, 24, etc), and radiological assessments were performed, this visit will be considered an EOT visit. Those subjects, for whom the radiological assessments were not performed, will need to attend the next scheduled 6 months visit, when radiological assessments (vertebral x-rays, DXA) will take place and an antibody sample will be taken. For these subjects this visit will be considered as EOT visit. For those subjects whose last regular study visit within 6 months (+ 45 days time window) prior to the PADCD was a 6 months visit (eg, month 6, 18, etc), the next regularly scheduled yearly study visit (eg, Q12M) within 6 months after PADCD will be considered an end of treatment visit. Data on fractures occurring between the last visit prior to PADCD and PADCD have to be collected via telephone or physical visits within six months after PADCD at the latest.

Subjects who withdraw from IP prior to the PADCD will continue to attend Q6M study visits for assessment of the primary and secondary end-point and safety. Subjects completing or discontinuing AIT will have the opportunity to remain on IP for at least 2 doses of IP after their last scheduled study visit during which they were still on AIT.

Subjects who withdraw full consent will have no further study assessments from that date forward.

7.16 End of Open-label Treatment

Subjects will complete an end of open-label treatment visit 30 to 45 days after the last dose of open-label denosumab either by clinic visit or telephone contact; assessments will be performed as described in Appendix A.

Subjects who withdraw from open-label denosumab early (see Section 8.1) will have follow-up data collected every 12 months following their regular follow-up schedule for up to approximately 66 months after PADCD.

7.17 Long-term Follow-up

Subjects will be followed for DFS, BMFS, and OS Q12M by clinic visits or telephone contacts starting from their last study visit (considered as EOT visit) for approximately 66 months after the PADCD. Following regulatory and IRB/IEC approval of Protocol Amendment 4, further data will be assessed (see Section 3.1).

Subjects who do not receive open-label denosumab will be followed for DFS, BMFS, and OS once a year (Q12M study visit) by clinic visits or telephone contacts until approximately 66 months after PADCD. Additionally, further data will be assessed (see Section 3.1).

Subjects who receive open-label denosumab will have Q6M on-site visits for administration of denosumab (60 mg SC Q6M) and (S)AE monitoring and will be followed Q12M only for DFS, BMFS, and OS until either approximately 66 months after PADCD or completion of treatment, whichever is longer. Additionally, further data will be assessed (see Section 3.1).

7.18 End of Study

The patient individual EOS is defined as the last formal visit or contact for a subject or an unscheduled study visit in case of early withdrawal from study.

End of Study reasons include three early EOS reasons (death, lost to follow-up, consent withdrawal) and per protocol EOS. At the end of study, the EOS CRF has to be completed for each subject.

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 her 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 take 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) should continue on the schedule of study observations as outlined in Appendix A.

Reasons for removal from investigational product/denosumab during the blinded phase and the OLP (see Sections 6.1.3 and 7.15):

- end of study
- completed investigational product/denosumab
- protocol deviation
- noncompliance
- adverse event
- disease progression[1]
- requirements for alternative therapy
- administrative decision

[1] Disease progression is defined as follows:
- distant metastases including supraclavicular lymph nodes (only from breast cancer). EOT decision related to infraclavicular lymph nodes has to be discussed with DMC.
- invasive local-recurrence (EOT decision to be discussed with DMC)
- DCIS ipsilateral EOT decision to be discussed with DMC)

Other disease outcome-related events relevant for the secondary endpoints, but not defined as disease progression are:
- invasive contralateral breast carcinoma
- second primary invasive non-breast carcinoma
- DCIS contralateral

- subject request
- pregnancy or breastfeeding
- other

8.2 Replacement of Subjects

Subjects will not be replaced.

9. ADVERSE EVENT 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)

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 initiation of investigational product.

Worsening of a pre-existing medical condition (eg, cancer, diabetes, migraine headaches, gout) should be considered an adverse event if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

Interventions for pretreatment conditions (eg, elective cosmetic 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.

9.1.2 Serious Adverse Events

A serious adverse event is defined by regulatory authorities as one that

- 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 excluding hospitalizations for anticipated protocol-specified procedures. However, prolongation of hospitalization or re-admission after a subject has been discharged would be considered a SAE.

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 SAE. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

9.2 Reporting Procedures for All Adverse Events During the Double-blind Phase

The investigator is responsible for ensuring that all adverse events (as defined in Section 9.1) observed by the investigator or reported by subjects after the signing of the informed consent through 30 days after the last dose of investigational product administration are reported using the applicable CRF. Adverse events that occur before randomization and are deemed by the investigator to be unrelated to study screening do not have to be recorded in the CRF.

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. The investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records or CRFs.

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 initiation of investigational product, the relationship of the adverse event to study screening is to be assessed by means of the 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 severity grading scale used in this study is described in 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. 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 attend all further scheduled study visits and be under medical supervision until symptoms cease or the condition becomes stable.

9.3 Serious Adverse Event Reporting Procedures During the Double-blind Phase

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 30 days after the last dose of investigational product administration are recorded in the subject's medical record and are submitted to Amgen. Reporting of serious adverse events that occur more than 30 days after the end of investigational product until end of study is at the investigator's discretion. The serious adverse events must be submitted to Amgen within 24 hours of discovery or notification of the event.

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 of receipt. 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 events must be consistent with that recorded on the applicable CRF (eg, Adverse Event Summary CRF).

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 SAE report form.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. 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 as required to regulatory authorities, investigators/institutions, and IRBs/ECs in compliance with all reporting requirements according to local regulations and GCP.

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

Any procedure planned prior to the signing of the informed consent resulting in an unforeseen worsening of the underlying pre-existing condition will not be considered a serious adverse event.

9.3.1 Adverse Events of Special Interest and Serious Adverse Event Reporting During the Open-label Phase

9.3.1.1 Adverse Events of Special Interest Reporting

[redacted]

observed by the investigator or reported by the subject after signing the ICF for the OLP through 30 days after the last dose of denosumab for subjects that receive denosumab in the OLP will be documented in the CRF. [redacted]

9.3.1.2 Serious Adverse Event Reporting

For subjects participating in the OLP and who receive denosumab, the investigator is responsible for ensuring that all SAEs observed by the investigator or reported by the subject that occur after signing of the ICF for the OLP through 30 days after the last dose of denosumab in the OLP are recorded in the subject's medical record and are submitted to Amgen (see Appendix F- Clinical Trial Serious Adverse Event report form) and recorded in the applicable CRF.

In addition any suspected atypical femoral fracture (femur midshaft fracture, femur subtrochanteric, femur distal) associated with minimal trauma will be classified as an SAE for ALL subjects, and should be recorded in the subject's medical record and submitted to Amgen (see Appendix F- Clinical Trial Serious Adverse Event report form) and recorded in the applicable fracture recording CRF. SAE reporting period for suspected atypical femoral fracture will be until end of study.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design

This is a multi-center, phase 3, randomized, double-blind, placebo-controlled study to determine the treatment effect of denosumab in subjects with breast cancer receiving aromatase inhibitor therapy. Approximately 3400 subjects will be randomized in a 1:1 ratio to receive either denosumab 60 mg or placebo SC Q6M in a blinded manner. The randomization schedule will be stratified by: type of hospital (major academic centers or other centers), prior AI usage (Y or N) and total lumbar spine BMD score at baseline (T-score < -1.0 or ≥ -1.0). Subjects will be recruited over an 82-month period. Subjects will remain on investigational product until the required number of events is reached and until they have had the opportunity to receive a minimum of at least 2 doses of IP, whichever occurs later. The PADCD is defined as:

- the time at which the required number of events (first clinical fracture) is reached and,
- all subjects have had the opportunity to receive at least 2 doses of IP

The primary objective is to determine whether denosumab compared to placebo will reduce the rate of first clinical fracture in women with non-metastatic breast cancer receiving aromatase inhibitor therapy. The secondary objectives are to assess the effect of denosumab compared to placebo on BMD at lumbar spine, total hip, and femoral neck in a subgroup of subjects at pre-selected sites; the incidence of new vertebral fractures (both morphometric and clinical); the incidence of new or worsening of pre-existing vertebral fractures (both morphometric and clinical); disease free survival; bone metastasis-free survival; overall survival; and to assess the safety and tolerability of denosumab in this population. [redacted]

The efficacy clinical hypothesis is that denosumab, when administered subcutaneously at a dose of 60 mg every 6 months, will be considered efficacious in subjects with non-metastatic breast cancer receiving AIT if the rate of first clinical fracture in

denosumab-treated subjects is lower than that in placebo-treated subjects. It is anticipated that denosumab will reduce the rate by 30% compared with placebo (ie, the true hazard ratio of denosumab compared with placebo is 0.70). The safety clinical hypothesis is that denosumab, when administered SC at a dose of 60 mg every 6 months, will be well tolerated in breast cancer subjects receiving AIT.

10.2 Study Endpoints, Subsets, and Covariates

10.2.1 Primary Endpoint

The time to the first clinical fracture. The power of the study to detect differences in this endpoint is described in Section 10.3.

10.2.2 Secondary Endpoints

Fracture-related secondary endpoints:

- The percent change in total lumbar spine, total hip and femoral neck BMD from baseline to 36 months (at pre-selected sites)
- Subject incidence of new vertebral fractures (morphometric fractures identified from on study x-rays and clinical vertebral fractures confirmed by x-rays) at month 36
- Subject incidence of a new or worsening of pre-existing vertebral fractures (morphometric vertebral fractures identified from on study x-rays and clinical vertebral fractures confirmed by x-rays) at month 36

Disease outcome-related secondary endpoints:

- DFS determined by the time from randomization to the first observation of disease recurrence or death from any cause
- BMFS determined by the time from randomization to the first observation of bone metastasis or death from any cause
- OS determined by the time from randomization to death from any cause

10.2.3 Safety Endpoints

- Subject incidence of treatment-emergent adverse events
- Clinically significant changes in laboratory values
- Subject incidence of anti-denosumab antibody (binding and neutralizing) formation

10.2.4 Exploratory Endpoints

[redacted]

[redacted]

10.2.5 Subsets

The principal analysis for the primary endpoint will be conducted on the full analysis set (FAS); analysis of the per-protocol population will be considered supportive. The FAS is defined as all subjects who are randomized. The per-protocol population is defined as all randomized subjects, with the correct diagnosis, no important protocol violations, and who received at least 1 dose of investigational product. Important protocol violations will be defined in the statistical analysis plan. The safety analysis set will consist of all subjects who were randomized and received at least 1 dose of investigational drug.

10.2.6 Covariates

The relationship of the following covariates to the primary and secondary efficacy endpoint will be explored:

- Type of hospital (grouped as major academic centers or other centers)
- Prior AI usage (Y or N)
- Total lumbar spine BMD score at baseline (T-score less than -1.0 or ≥ -1.0)
- Age (Age will primarily be considered as a continuous variable however, if appropriate, the age may be categorized so that an equal number of subjects are in each category)
- The following covariates are specific to the endpoints DFS, BMFS, and OS:
  - Breast tumor size
  - Lymph node status
  - Histopathologic grading of the breast tumor and tumor type
  - Breast cancer therapy
  - Hormone receptor (ER/PgR) status / Endocrine therapy
  - Human Epidermal growth factor Receptor 2 (HER-2) status / HER-2 targeted therapy
- Other covariates reported in literature as important or from other ongoing Amgen studies will be considered in the analysis if considered appropriate at the time of analysis.

10.3 Sample Size Considerations

Approximately 3400 subjects will be enrolled into this trial (1700 per treatment group), which will conclude once approximately 247 subjects have experienced a clinical

fracture. This assumes based on current recruitment and recruitment projections that there will be an 82-month accrual period and on a drop-out rate of 3.6% per year.

Approximately 247 subjects must experience a clinical fracture for this study to have 80% power to detect a fracture ratio of 0.70 (denosumab vs. control) with a two-sided significance level of 0.05. A hazard ratio of 0.70 indicates that the fracture rate in the denosumab group is 30% less than in the control group (ie, 1.39% per year).

The incidence of clinical fracture in the ATAC trial (Jakesz et al, 2005) was 22.6 per 1000 subject-years. From this the fracture rate in the control group has been estimated at 2.43% per year. In study 20050209, the observed total fracture rate of both arms combined after 61 months is 1.7% per year. Assuming a hazard ratio of 0.70, the fracture rate in the control group is expected to be about 2.0% per year. According to this fracture rate, 247 fractures will be reached after 103 months. All subjects will be followed until they have had the opportunity to receive at least 2 doses of IP.

All clinical fractures, except those of the skull, face, fingers, and toes, which are typically not associated with osteoporosis, will be included in the analysis of clinical fractures.

The key secondary endpoint analysis is a comparison of the percent change of lumbar spine BMD between the denosumab treatment and placebo groups. In a subset of the ATAC data (Eastell and Adams, 2002) a 1.8% difference was observed between the change from baseline to 12 months in the tamoxifen and anastrozole groups. To have 90% power to detect a 1.8% difference (SD = 3.9%) between denosumab and placebo in the percentage of change of BMD for lumbar spine at 12 months with a two-sided significance level of 0.05, it will be necessary to have BMD data from 102 subjects per treatment arm.

10.4 Access to Individual Subject Treatment Assignments

This is a double-blind study. Subject treatment assignments will remain blinded to investigator, subjects and Amgen in order to reduce bias. The external DMC will have access to subject treatment assignments. To minimize the potential introduction of bias, these individuals will not have any direct contact with the study site personnel or subjects.

The identity of investigational product assigned to subjects or to individual boxes of investigational product will be contained in 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.

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 is strongly encouraged to contact the Amgen 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 CRF.

Subjects eligible to receive denosumab in the OLP will be unblinded as detailed in Section 5.

10.5 Interim Analysis, Early Stopping Guidelines, and Time-points of Analyses

An external DMC will be formed with members consisting of individuals chosen for their expertise in oncology and bone disease. Selected ABCSG and Amgen staff may serve as liaisons to the external DMC, but will not be voting members, and will not be unblinded to the results. The DMC will have access to subject's individual treatment assignments. To minimize the potential introduction of bias, these individuals will not have any direct contact with the study site personnel or subjects. Members of this external DMC will include, at a minimum, physicians external to Amgen and appropriate statistical representation external to Amgen. The DMC will meet approximately annually. Records of all meetings will be archived. The DMC will communicate major safety concerns and recommendations regarding study modification or termination to Amgen senior management. Details regarding the DMC will be provided in a separate DMC Charter.

This DMC will review unblinded safety data. Safety analyses provided to the DMC will be descriptive in nature.

There will be no interim analysis based on the primary endpoint. An interim analysis for futility for the secondary endpoint DFS was performed after PADCD by an independent statistician. This interim analysis used an informal futility bound. Study termination may be recommended by the DMC if the observed hazard ratio exceeded the hazard ratio for futility (0.85). Following review of the interim DFS analysis results, the DMC determined that the hazard ratio did not indicate futility and that the study should continue further for approximately 66 months. In addition, the DMC recommended that a time-driven analysis for efficacy of the secondary endpoint DFS should be performed at

approximately 18 months after PADCD, before any investigator/subject level unblinding occurred for entry into the OLP.

The primary analysis will take place after PADCD when all subjects attended their last study visit (considered as EOT visit). The primary analysis includes the primary endpoint and the first three secondary endpoints concerning the changes in BMD and vertebral fractures.

A final exploratory [redacted] analysis as well as the main analyses for efficacy of the secondary endpoints BMFS and OS will be performed at the end of the **main** study.

Additionally, [redacted] will be evaluated in a final exploratory analysis at this time point. **Only data collected up to the EOS visit (end of OL treatment visit or their last scheduled LTFU visit) will be included in the final analysis. Any data collected from the ZA substudy will be excluded.**

10.6 Planned Methods of Analysis

10.6.1 General Approach/Considerations

The principal analysis for the efficacy endpoints will be conducted on the FAS and the per protocol population approach will be considered supportive. Safety analyses will be conducted on the safety analysis set.

Where the protocol specifies multiple baseline measurements to be taken, the mean of the baseline records will be used for computation of change from baseline endpoints. Otherwise, baseline will be taken as the observation recorded just prior to first dose of investigational product.

For time to event variables, Kaplan-Meier curves (Kaplan and Meier, 1958) will be estimated and graphically displayed. The hazard ratio and its corresponding 95% CI will be estimated using Cox Model.

Continuous variables will be summarized descriptively using mean, standard deviation, minimum, and maximum. Median and other selected percentiles will be substituted for mean and standard deviation for parameters exhibiting a lack of normality.

Frequencies and percentages will be presented for categorical variables.

The primary analysis for fracture-related endpoints will take place when for all subjects, data on clinical fractures occurring prior to PADCD have been collected via telephone or physical visits within six months after PADCD at the latest. The analysis of DFS will be

performed at approximately 18 months after PADCD (following DMC review of the DFS interim analysis). Analysis of the disease outcome-related secondary endpoints BMFS and OS will be performed at the end of the study.

The primary and secondary null hypotheses will be tested using the hierarchical analysis strategy and the Hochberg procedure to control the overall significance level of 0.05. The DFS analysis at approximately 18 months after PADCD will be considered the main DFS analysis for the hierarchical testing strategy, with the f[redacted].

The primary null hypothesis will be tested first at a significance level of 0.05. If the primary hypothesis is rejected, the secondary null hypotheses will be tested in a stepwise fashion over 6 steps at a significance level of 0.05. In case any one of the hypotheses is not rejected at a previous step, all subsequent endpoints will be analysed in a descriptive manner only. Some steps involve single null hypothesis and some involve multiple null hypotheses. If there are multiple null hypotheses, the Hochberg procedure will be used to control for multiplicity and the testing will proceed to the next step only if all null hypotheses are rejected. These steps will involve the secondary null hypotheses for the following endpoints:

Fracture-related secondary endpoints:

A. Percent change in total lumbar spine, total hip and femoral neck BMD from baseline to month 36 (at pre-selected sites)
B. Subject incidence of new vertebral fractures (morphometric vertebral fractures identified from study x-rays and clinical vertebral fractures confirmed by x-ray) at month 36
C. Subject incidence of a new or worsening of pre-existing vertebral fractures (morphometric vertebral fractures identified from on study x-rays and clinical vertebral fractures confirmed by x-rays) at month 36

Disease outcome-related secondary endpoints:

D. Disease-free survival is defined as any evidence of disease recurrence or death from any cause
E. Bone metastasis-free survival determined by the time to first occurrence of bone metastasis (either symptomatic or asymptomatic) or death from any cause
F. Overall survival

Statistical analysis procedures and techniques will be reviewed in the light of current practice and new techniques, prior to breaking treatment blind, and if appropriate alternative newer technical procedures will be adopted.

10.6.2 Analysis of Key Study Endpoints

10.6.2.1 Efficacy Analysis

Primary Endpoint

The time to first on-study clinical fracture will be defined as the number of days from randomization to the date of the x-ray confirming the clinical fracture. Subjects who die or withdraw without experiencing a clinical fracture will be censored at the date of last contact or study termination whichever is earlier. Only clinical fractures which occur prior to PADCD will be included in the analysis for the primary endpoint. The primary analysis will use a Cox model (Cox, 1972) including treatment groups as the independent variable and stratified by the randomization stratification factors.

[redacted] Summary statistics will include the hazard ratio of denosumab compared with placebo and 95% CI; estimated fracture rates at 36 months and 95% CI using Kaplan-Maier method; crude incidences at the End of Study and 95% CI; differences between fracture rates and 95% CI.

Sensitivity analyses will be performed using the primary analysis method. The first sensitivity analysis will consider the subjects who withdraw from the trial due to a > 10% loss of BMD in the lumbar spine over any 1-year period as having had a clinical fracture at the time of withdrawal. This will assess if study monitoring has resulted in informative censoring of subjects within the trial. A second sensitivity analysis will be conducted on the per protocol population to assess the effect of non-protocol compliant subjects. The primary analysis will consider all available subject data regardless of the subjects time since last treatment with study drug, a third sensitivity analysis will consider the influence of subject experience subsequent to discontinuation from study treatment. If any of the sensitivity analyses cause conflicting results to the primary analysis then similar sensitivity analyses will be conducted for the secondary related to BMD and fracture.

Secondary Endpoints

The presence or absence of a new vertebral fracture (morphometric vertebral fractures identified from on study x-rays and clinical vertebral fractures confirmed by x-rays) will

be noted at 36 months (over a 36 month evaluation period). The primary analysis of this endpoint will use logistic regression models including treatment groups as the independent variable and stratified by the randomization stratification factors.

[redacted].

The percent change in lumbar spine, total hip and femoral neck BMD from baseline to 36 months will be calculated for subjects at pre-selected sites. The primary analysis of these endpoints will employ a mixed effects model (Longford, 1993) including treatment groups as the independent variable and stratified by the randomization stratification factors. [redacted].

Disease-free survival is defined as time to any evidence of local or distant metastases, contra-lateral breast cancer, secondary carcinoma, or death from any cause. Bone metastases-free survival is determined by the time to first occurrence of bone metastases (either symptomatic or asymptomatic) or death from any cause. These endpoints and OS will be analyzed using the same methods as used in the analysis of the primary endpoint. [redacted].

10.6.2.2 Safety Analyses

Safety data will be summarized for all subjects who receive at least 1 dose of investigational products. All AEs 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 Summary CRF pages. The analysis of adverse events will be descriptive. The subject incidence rates of treatment-emergent adverse events reported during the study period will be tabulated by system organ class and preferred term. Additional summary tables will be provided separately for serious adverse events, CTCAE grade 3, 4, or 5 AEs, 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, SAEs, CTCAE grade 3, 4 or 5 adverse events, and adverse events leading to study withdrawal will be summarized in the same manner as treatment-emergent adverse events. All adverse events, CTCAE grade 3, 4, or 5 adverse events, serious adverse events, all investigational product related adverse events, investigational product related CTCAE grade 3, 4, or 5 AEs, and investigational product related serious adverse events will also be summarized.

The subject incidence rates of [redacted] reported during the OLP will be tabulated separately by system organ class and preferred term.

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 (CTCAE version 3.0) in recorded values from baseline to "worst" on-study value is displayed. Graphical representations of aggregate data may also be presented for parameters of interests.

Incidence of fatal adverse events will be summarized for all enrolled subjects.

10.6.2.3 Anti-denosumab Antibodies

The incidence and percentages of subjects who develop binding and neutralizing anti-denosumab antibodies at any time will be tabulated by treatment group and visit.

10.6.2.4 Exploratory Analyses

[redacted]

11. INVESTIGATIONAL PRODUCT

11.1 Denosumab

Blinded phase

Denosumab may be provided as either of the 2 following formulations: 1) as a sterile, clear, colorless to slightly yellow, preservative free liquid in blinded-label glass vials; 2) as a prefilled syringe (PFS) as a sterile, single use, preservative free solution for subcutaneous injection. The vial formulation is 60 mg denosumab per mL of [redacted] mM Sodium Acetate, [redacted]% sorbitol, with a pH of [redacted]. The PFS formulation contains 60 mg/mL denosumab, [redacted] mM acetate ([redacted] mg/mL), [redacted]% ([redacted] mg/mL) sorbitol and [redacted]% ([redacted] mg/mL) polysorbate 20 at a pH of [redacted]. The PFS is filled to a target deliverable volume of [redacted] mL. Placebo will be supplied in matched containers and the formulation will be identical to denosumab with the exception of the protein content.

The box number of investigational product is to be recorded on each subject's investigational product administration CRF.

Unique boxes will be assigned for each dose the subject will receive while on study. To obtain box number assignment for a schedule dose, site personnel should call the IVRS.

Refer to Sections 10.4 and 11.2 for conditions and requirements for unblinding.

Investigational product details for denosumab including labeling, storage, preparation, etc., are provided in the Pharmacy Guide, Appendix C.

Open-label phase

Denosumab will be provided as a PFS as a sterile, single use, preservative free solution for subcutaneous injection. The PFS formulation contains 60 mg/mL denosumab, [redacted] mM acetate ([redacted] mg/mL), [redacted]% [redacted] mg/mL) sorbitol and [redacted]% ([redacted] mg/mL) polysorbate 20 at a pH of [redacted]. The PFS is filled to a target deliverable volume of 1.0 mL.

Boxes should be selected from the Amgen supplied stock.

Product details for denosumab including labeling, storage, preparation, etc are provided in the Pharmacy Guide.

11.2 Access to Treatment Assignments

11.2.1 Blinded phase

The identity of investigational product assigned to subject numbers or to individual boxes of investigational product will be available for emergency situations through an 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.

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 is strongly encouraged to contact the Amgen 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 CRF.

11.2.2 Open-label Phase

The opportunity to start with open-label denosumab will be open for 12 months following Protocol Amendment 4 regulatory and IRB/IEC approval, which will be after the disease outcome-related endpoint analysis performed approximately 18 months after PADCD.

After the ICF is signed, unblinding of subjects thought eligible for denosumab treatment in the OLP can occur, and the first dose of denosumab shall be administered within 8 days of unblinding.

11.3 Compliance in Investigational Product Administration

When investigational product is dispensed for administration to the subject during a study, the investigator or responsible person will determine the level of compliance with the administration of the investigational product. The subject's investigational product

compliance (eg, amount used) will be recorded on the investigational product administration case report form.

12. REGULATORY OBLIGATIONS

12.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population. Amgen will discuss updates with ABCSG and after an agreement Amgen will provide the template to ABCSG who will disseminate the information to the investigators.

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 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.

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 or legally acceptable representative 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, other written subject information, and any proposed advertising material must be submitted to the IEC for written approval. For each participating site, ABCSG must receive a copy of the written

approval of the protocol and informed consent form before recruitment of subjects into the study and shipment of investigational product.

The investigator must submit and, where necessary, obtain approval from the IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IEC 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 renewal throughout the duration of the study as applicable. Copies of the investigator's reports and the IEC continuance of approval must be filed in the study files.

12.3 Prestudy Documentation Requirements

The investigator is responsible for forwarding the following documents to Amgen for review before investigational product is shipped:

- Signed and dated protocol signature page (Investigator's Agreement)
- Copy of approved informed consent form and subject information sheet
- Copy of the IEC approval of the protocol, consent form, and subject information sheet
- Up-to-date curricula vitae of principal investigator and all co/subinvestigators
- IEC composition and/or written statement that IEC is in compliance with regulations
- Current subject/investigator indemnity insurance
- Signed study contract
- Completed Financial Disclosure Form
- Other country-specific forms, as defined in the country-specific requirements

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/ABCSG, subjects should be identified by the subject study number only. Documents that are not for submission to Amgen/ABCSG (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with local regulatory requirements 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 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 her study-related records without violating the confidentiality of the subject.

12.5 Investigator Signatory Obligations

Each clinical study report should be signed by the investigator or, in the case of multicenter studies, 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

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. The IEC must be informed of all amendments and give approval. ABCSG must send a copy of the approval letter from the IEC 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 in writing of the study's completion or early termination and send a copy of the notification to Amgen.

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 reserves the unilateral right, at its 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.

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 **ABCSG** Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's case report form 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 and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed informed consent forms and subject identification list. **Documentation of CRFs is visible via web-based electronic data capture (EDC) system at any time during the study. At database closure data will be provided on compact discs for filing purposes.**
- 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 and Amgen
- 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

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

No study document should be destroyed without prior written agreement between Amgen 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 in writing of the new responsible person and/or the new location.

13.3 Study Monitoring and Data Collection

The Amgen 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, case report forms and other pertinent data) provided that subject confidentiality is respected.

The ABCSG monitor is responsible for verifying the case report forms at regular intervals 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 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.

Due to an unexpected change of the data management system, the **Interface** DATAPORT/**TRIALDATAPORT** (**EDC system** MACRO, provided by InferMED), has replaced "IntTrial®". The current **EDC system**, enables the investigator to work on a web-based online documentation (e-CRF).

MACRO provides communication tools which will help users to manage discrepancies electronically, to conduct source data verification and to improve communication within the study team.

- 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 ABCSG. 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 raised via EDC for site completion.
- The principal investigator will sign only the **Confirmation of Data Form**. These signatures will indicate that the principal investigator inspected or reviewed the CRF, the data queries, and the site notifications, and agrees with the content. Paper output of the **CRF can be printed out (tabular format) by the investigator whenever needed.**
- ABCSG's clinical data management department will ensure that the database is corrected for the following CRF issues without notification to site staff:
  - Formal corrections (eg, 12.01.2012 -> 12/01/2012, 1 per day -> 1/day)
  - misspellings that do not change the meaning of the word (excluding adverse events and medications)
  - location of data recorded on an incorrect CRF (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
  - administrative data (eg, event names for unscheduled visits or retests)
  - if both the end date and a status of continuing is indicated (eg, for adverse events, concomitant medication, hospitalization), the end date will supersede
  - If equivalent units or terms are recorded instead of the acceptable Amgen standard (eg, cc for mL, SQ for SC route, Not Examined for Not Done), the Amgen 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 CRF page numbers

A detailed description of further items for corrections without notification to site staff **is** given in the r**espective** Data Management Plan (DMP).

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 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 Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2004), 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.
- 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 for corporate review. The Clinical Study Agreement among the institution, principal investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

13.6 Compensation

Subject 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.

14. REFERENCES

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15. APPENDICES

Appendix A. Schedule of Assessments for Blinded and Open-label Treatment Phases

Study Assessments	Screening	Treatment Phase			End of treatment (EOT) [10]	Long Term Follow-up (Q12M) [11]	Early End of Study (EOS) [12]
		Study Day 1 (-35 days)	Month 6, 18, 30, 42, etc	Month [10] 12, 24, 36, 48, etc			
Medical and Medication History	X						
Physical examination, including vital signs [1]	X		X	X	X		X
ECOG Performance status	X		X	X	X		X
Investigational product administration		X	X	(X)			
Vertebral X-ray [2]	X [8]			X	X		X
[redacted]							
Bone Scan [4]	X [9]						
Hematology	X		X	X	X		X
Serum Chemistry	X		X	X	X		X
Pregnancy Test [5]	X						
Denosumab Antibody Assay [6]	X			(X)	X		
[redacted]							
Adverse Events	X	X	X	X	X		X
Clinical Fracture Recording [7]		X	X	X	X		X
Survival (DFS, OS BMFS)						X	X

Reference Number	Footnote
1	Screening physical exam may be waived if subject has had physical exam performed as standard of care within 30 days prior to signing informed consent
2	X-rays are performed at baseline, 12M, 24M, 36M and EOT visits. Between the 36M and the EOT visit, vertebral X-rays may be performed based on the investigator's decision and according to local routine practice. Unscheduled X-rays may be performed when significant clinical symptoms (e.g. back pain) are reported
[redacted]	[redacted]
5	A pregnancy test, where applicable, must be performed within 7 days prior to randomization. Where post-menopausal status is clearly documented, a pregnancy test is not required (see inclusion and exclusion criteria for definition of post-menopausal status).
6	Antibody samples will be collected at baseline and end of treatment
7	X-rays and radiologists report will be collected.
[redacted]	[redacted]
10	Treatment phase, Q12M visits: At PADCD, the last yearly visit will be considered the End of Treatment (EOT) visit. Subjects will undergo EOT assessments as follows: For subjects, whose last regular study visit within 6 months (+45 days time window) prior to the PADCD was a yearly visit (eg, month 12, 24, etc), this visit will be considered an EOT visit. An antibody sample will be taken during the first visit of the Long-Term Follow-Up. All subjects, whose last regular study visit within 6 months (+45 days time window) prior to the PADCD was a 6 months visit (eg, month 6, 18, etc), will have to attend the next regularly scheduled yearly study visit (eg, Q12M) within 6 months after PADCD at the latest and perform all corresponding assessments, including antibody sampling. Subjects who withdraw from IP prior tot he PADCD will continue to attend Q6M study visits for assessment of the primary and secondary end-point and safety until PADCD and will then enter the Long-Term Follow-Up; and subjects who withdraw full consent (=EOS) will have no further study assessments from that date forward. All adverse events and serious adverse events must be reported from signing of the ICF through 30 days after the last dose of Investigational Product.
11	Long-Term Follow-Up (LTFU): Subjects will be followed-up once a year (Q12M) for overall survival (OS) and disease-free survival (DFS) by clinic visits or telephone contacts starting from their last study visit (considered as EOT visit) until either **approximately** 66 months post PADCD, depending on an interim DFS analysis at PADCD. To avoid extensive simultaneous visits or contacts each year.
12	Early End of Study (EOS): the last formal visit or contact for a subject, or an unscheduled study visit in case of early withdrawal from study (withdrawal of informed consent). If a subject reaches EOS per protocol, the EOS visit will occur during the LTFU, and only a survival assessment (DFS, OS, BMFS) is required.

Schedule of Assessments for Open-label Phase

Study Assessments	Open Label Phase - Subjects receiving open label denosumab				
	Visit 1	Q6M Visits	Q12M visits	End of open label treatment	Q12M visits (after End of treatment)[1]
Investigational product administration[2]	X	X	X		
Concomitant Medications[3]			X		X
Collection of (S)AEs of special interest (oral events) and SAEs[4]		X	X	X	
Clinical Fracture Recording[5]			X		X
Survival (DFS, OS, BMFS)			X		X
DXA[6]					

Long Term Follow up - Subjects not receiving open label denosumab	
Study Assessments	Q12M visits
Concomitant Medications[3]	X
Clinical Fracture Recording[5]	X
Survival (DFS, OS, BMFS)	X
DXA[6]	

Reference Number	Footnote
1	Subjects who receive open label denosumab will be followed Q12M until either approximately 66 months after PADCD or until the completion of treatment whichever is longer
2	Subjects who receive open label denosumab will receive up to 3 years (maximum of 7 doses) of IP
3	Concomitant bone affecting medication (Bone targeted therapy (e.g. bisphosphonate or denosumab), Glucocorticoids, Antiepileptic Drug, Antidepressants and Insulin), anti-cancer related therapy (e.g. chemotherapy or endocrine therapy) and Supplements (Vitamin D and calcium) will be collected for all subjects
4	Adverse events of special interest (all oral events for ONJ adjudication) will be recorded in the eCRF from informed consent to 30 days after the last dose of denosumab. SAEs that occur from informed consent to 30 days after the last dose of denosumab will be recorded in the CRF and reported to Amgen.
5	Any suspected atypical femoral fracture (femur midshaft fracture, femur subtrochanteric, femur distal) associated with minimal trauma will be classified as an SAE for all subjects and should be recorded in the CRF and reported to Amgen.
6	For all subjects whenever a DEXA scan is performed as standard of care during the open label phase and follow up phase, these data will be collected in the CRF

Appendix B. Adverse Event Assessments

Adverse Event Relatedness

Is there a reasonable possibility that the event may have been caused by investigational product? No___ Yes___

The descriptions provided below will help guide the principal investigator in making the decision to choose either "yes" or "no":

No = There is not a reasonable possibility that the event may have been caused by investigational product.

The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject's clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when investigational product is re-administered
- does not follow a temporal sequence from administration of investigational product

Yes = There is a reasonable possibility that the event may have been caused by investigational product.

The adverse event:

- follows a temporal sequence from administration of investigational product
- is a known response to the investigational product based on clinical or preclinical data
- could not be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of investigational product
- reappears or worsens when investigational product is readministered

Adverse Event Severity Scoring System

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

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

Appendix C. Pharmacy Guide

Open-Label Extension

Denosumab will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical trial drug distribution procedures.

Denosumab will be provided as a sterile, colorless to slightly yellow, preservative-free solution in a 1 mL pre-filled syringe (PFS). The formulation is 60 mg/mL denosumab, [redacted] mM sodium acetate ([redacted] mg/mL), [redacted]% ([redacted] mg/mL) sorbitol, [redacted]% polysorbate 20, pH [redacted]. Each PFS is intended for single use only. One PFS will be packaged per box.

Denosumab should be taken from the Amgen supplied stock held at the site. Please ensure the correct quantity is selected.

Labeling

Each single-use pre-filled syringe of denosumab will be labeled in accordance with Annex 13. Information presented on the label for study medication will comply with the local regulatory requirements.

Storage

The boxes containing denosumab will be stored at the investigational site at 2 C to 8°C. Prefilled syringes are to be kept in the box until the time of use. Exposure of the material to temperatures outside these limits may result in a loss of activity. Amgen Inc. or its designee must be notified if any test material is exposed to excessive or uncontrolled temperatures, in which case possible replacement of the material will be considered.

Actual storage conditions records during the period of the study must be maintained and include the date, time and initials of the person checking on the "working day" temperatures of the refrigerator used for the storage of trial supplies. Continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording shall also be maintained.

Preparing the Subcutaneous Injections

One denosumab pre-filled syringe should be removed from the refrigerator and brought to room temperature. Once removed from the refrigerator, the pre-filled syringe must be used within 24 hours. There are no other special preparations required prior to investigational product administration.

Supply and Return of Drug

At the start of the OLP and as needed thereafter, denosumab will be shipped to the responsible person (eg, a pharmacist) at the investigator's institution, who will check the amount and condition of the drug and enter these data into the Proof of Receipt Form. The Proof of Receipt Form should then be returned to Amgen, and the original retained at the site.

Amgen recommends that sites destroy used and unused product if local capabilities and regulations permit. If this is not permissible, at the end of the study, or as directed, unused containers, will be returned to Amgen or designee. The Return of Investigational Product for Destruction Form must be completed and included in any shipment of unused investigational product to Amgen or designee. Used pre-filled syringes will be disposed at the clinical sites using site standards.

Investigational Product Accountability

An Investigational Product Accountability Record for the investigational products is mandated by the protocol, must be kept current and should contain:

- the dates and quantities of denosumab received from Amgen
- packaging lot number for product received
- subject's identification (subject number)
- date denosumab dispensed
- the initials of the dispenser

These inventories must be made available for inspection by an authorized Amgen representative or designee and regulatory agency inspectors. The investigator is responsible for the accountability of all used and unused trial supplies.

Double-blind Treatment Phase Packaging and Formulation

Denosumab will be manufactured and packaged by Amgen Inc and distributed using Amgen clinical trial drug distribution procedures.

Denosumab may be provided as either of the 2 following formulations: 1) as a sterile, clear, colorless to slightly yellow, preservative free liquid in blinded-label glass vials; 2) as a prefilled syringe (PFS) as a sterile, single use, preservative free solution for subcutaneous injection. The vial formulation is 60 mg denosumab per mL of [redacted] mM Sodium Acetate, [redacted]% sorbitol, with a pH of [redacted]. The PFS formulation contains 60 mg/mL denosumab, [redacted] mM acetate ([redacted] mg/mL), [redacted]% ([redacted] mg/mL) sorbitol and [redacted]%

([redacted] mg/mL) polysorbate 20 at a pH of [redacted]. The PFS is filled to a target deliverable volume of 1.0 mL. Placebo will be supplied in matched containers and the formulation will be identical to denosumab with the exception of the protein content.

Investigational product will be packaged in boxes as individual patient kits containing single-use vials or pre-filled syringes of denosumab or matching placebo. Each kit of investigational product will be coded alphanumerically for treatment assignment.

Unique boxes will be assigned for each dose the subject will receive while on study. To obtain box number assignment for a scheduled dose, site personnel should call the IVRS vendor. The box number of investigational product is to be recorded on each subject's Investigational Product Administration case report form. In addition, the subject's identification number, randomization identification number and box number must be written on all appropriate drug accountability and dispensing records.

The identity of investigational product assigned to subject numbers or to individual boxes of investigational product will be contained in 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. 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 is strongly encouraged to contact the Amgen 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 case report form.

Investigational Product Single Use Vial

Labeling

Each single-use vial of denosumab or placebo will be labeled in accordance with Annex 13. Information presented on the label for study medication will comply with the local regulatory requirements.

Storage

The boxes containing denosumab or placebo will be stored at the investigational site at 2 C to 8°C. Vials are to be kept in the box until the time of use. Exposure of the material to temperatures outside these limits may result in a loss of activity. Amgen, Inc. or its

designee must be notified if any test material is exposed to excessive or uncontrolled temperatures, in which case possible replacement of the material will be considered.

Actual storage conditions records during the period of the study must be maintained and include the date, time and initials of the person checking on the "working day" temperatures of the refrigerator used for the storage of trial supplies. Continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording shall also be maintained.

Preparing the Subcutaneous Injections

One investigational product vials should be removed from the refrigerator and brought to room temperature. One 1.0 mL syringe should be used to prepare the dose. There are no other special preparations required prior to investigational product administration.

Investigational Product Single Use Pre-filled Syringe

Labeling

Each single-use pre-filled syringe of denosumab or placebo will be labeled in accordance with Annex 13. Information presented on the label for study medication will comply with the local regulatory requirements.

Storage

The boxes containing denosumab or placebo will be stored at the investigational site at 2 C to 8°C. Pre-filled syringes are to be kept in the box until the time of use. Exposure of the material to temperatures outside these limits may result in a loss of activity. Amgen, Inc. or its designee must be notified if any test material is exposed to excessive or uncontrolled temperatures, in which case possible replacement of the material will be considered.

Actual storage conditions records during the period of the study must be maintained and include the date, time and initials of the person checking on the "working day" temperatures of the refrigerator used for the storage of trial supplies. Continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording shall also be maintained.

Preparing the Subcutaneous Injections

One investigational product pre-filled syringe should be removed from the refrigerator and brought to room temperature. There are no other special preparations required prior to investigational product administration.

Supply and Return of Drug

At study initiation and as needed thereafter, investigational product will be shipped to the responsible person (eg, a pharmacist) at the investigator's institution, who will check the amount and condition of the drug and enter these data into the Proof of Receipt Form. The Proof of Receipt Form should then be returned to Amgen, and the original retained at the site.

The person responsible for receiving the drug shipment will also need to contact the IVRS vendor to confirm receipt of investigational product.

At the end of the study, or as directed, all investigational product supplies, including unused, partially used, or empty containers, will be returned to the Amgen or designee, except used pre-filled syringes. Used pre-filled syringes will be disposed at the clinical sites using site standards.

Investigational Product Accountability

An Investigational Product Accountability Record for the investigational products mandated by the protocol must be kept current and should contain:

- the dates and quantities of investigational product received from Amgen
- packaging lot number AND box numbers for product received
- subject's identification (subject number and initials)
- date and box number of investigational product dispensed
- the initials of the dispenser

The Return of Investigational Product for Destruction Form must be completed and included in the shipment of used and unused investigational product to Amgen or designee.

These inventories must be made available for inspection by an authorized Amgen representative or designee and regulatory agency inspectors. The investigator is responsible for the accountability of all used and unused trial supplies.

Calcium and Vitamin D Supplements

Calcium and vitamin D supplements will not be provided by Amgen. They should be obtained from suppliers approved by the pharmacy of the individual institution. These drugs will be formulated, packaged, labeled, and stored according to local manufacturer, supplier, and institutional procedures. The investigator will be responsible for obtaining supplies of these drugs.

Appendix D. 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: _____

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.

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Appendix E. Classification Eastern Cooperative Oncology Group (ECOG) Performance Scale

ECOG Scale		Performance Status
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.

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 F. Serious Adverse Event Form

AMGEN ABCSG-18 20050209	Clinical Trial Serious Adverse Event Report – Phase 1–4 *Notify Amgen Within 24 Hours of knowledge of the event*	☐New ☐Follow-up

SELECT OR TYPE IN A FAX#

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth Day Month Year	Sex ☐F ☐M	Race

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

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? If yes see section 10 No ✓	 Yes ✓	Relationship Is there a reasonable possibility that the event may have been caused by an Amgen device? No ✓	 Yes ✓	 If Yes, what device?	Outcome of Event 01 Resolved 02 Resolving 03 Not resolved 04 Fatal	Check only if event is related to study procedure eg, biopsy

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required hospitalization; 04 Prolonged hospitalization; 05 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 07 Other significant medical hazard

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized? ☐No ☐Yes, if yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	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
<<IMP>> ☐✓Blinded ☐✓Open Label						

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant 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 ✓

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AMGEN ABCSG-18 20050209	Clinical Trial Serious Adverse Event Report – Phase 1–4 *Notify Amgen Within 24 Hours of knowledge of the event*	☐New ☐Follow-up

Site Number	Subject ID Number

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:

Test / Unit / Date (Day Month Year)										

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)* For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee	Title	Date

Appendix G. Zoledronic Acid Substudy

1. EXPLORATORY OBJECTIVE

[redacted]

2. RATIONALE

Denosumab cessation is associated with declines in bone mass that approach pre-treatment levels and available data do suggest an increase in multiple vertebral fractures after discontinuation. Bisphosphonate treatment after denosumab may be warranted to potentially prevent these fractures, particularly in patients not previously exposed to bisphosphonates and who remain at high fracture risk (ie, osteoporosis with previous vertebral fractures), but limited data are available confirming the validity of this hypothesis. Therefore, there is a data gap regarding optimal strategies for patients who will discontinue denosumab. The ZA substudy is designed to evaluate subjects completing open-label denosumab treatment, to either receive a single dose of ZA, or to be managed according to current standard of care (SOC) for respective patient population. Standard of Care (SoC) for this substudy patient population depends on individual factors such as bone density, lifestyle recommendations by the Investigator such as diet, physical activities and sun exposure, as well as local treatment standards and will be agreed upon with the treating Investigator.

There are currently no guidelines or evidence regarding the best strategy to be considered when discontinuing denosumab in cancer treatment-induced bone loss. There has been expert opinion published stating that a transition to a bisphosphonate represents a treatment option (Hadji et al, 2017).

3. EXPERIMENTAL PLAN

3.1. Substudy Design

[redacted]

After regulatory and IRB/IEC approval of Protocol Amendment 6 (added ZA substudy), willing and eligible subjects who participated in the OLP of the study

and completed OL denosumab may opt in this ZA substudy and either receive a single dose of ZA (Therapy Arm), or are managed according to the current SOC for this patient population (Control Arm). Subjects who completed OLP denosumab are eligible to participate in the ZA substudy as long as the outlined criteria are fulfilled.

Written consent may be obtained from date of the last OLP denosumab administration until 9 months after. The screening phase starts from date of the last OLP denosumab administration at the earliest and lasts until randomization, but must occur after written consent has been obtained.

Willing and eligible subjects who completed OL denosumab are randomized to 1 single 5 mg IV dose of ZA or to SOC. Randomization can be performed within 8 days prior to Day 1. Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit. Follow up will continue for a total of 18 months after day 1. Randomization will be stratified by AI use at the timepoint of OLP denosumab completion (Yes or No).

After day 1, subjects will be evaluated every 6 months. DXA scan can be performed between 7 to 9 months after the date of the last denosumab administration, but in any case before the date of first ZA administration. Routine DXA scans performed within the outlined time window can be used as baseline DXA scans.

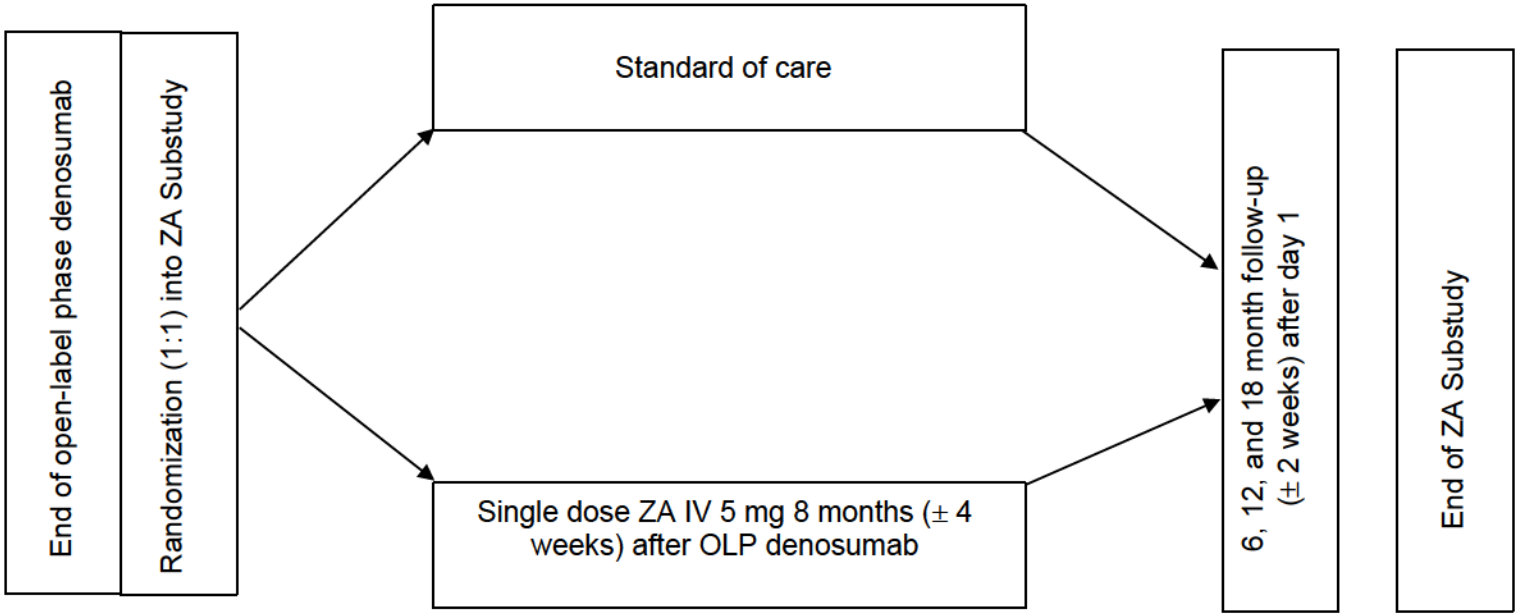
Subjects who do not fulfill the eligibility criteria for or do not consent to the ZA substudy will complete OLP assessments only.

Subjects who participate in the ZA substudy, will undergo the following assessments:

[redacted]

3.2. Schema

ZA Substudy Design and Treatment Schema



IV = intravenous; ZA = zoledronic acid.

3.3. Number of Centers

Approximately 30 sites in Austria are anticipated to participate in the ZA substudy.

3.4. Number of Subjects

Approximately 200 subjects are anticipated to participate in the ZA substudy.

3.5. Estimated Substudy Duration

3.5.1. Estimated Substudy Duration for Participants

Subjects will be in this substudy for a maximum duration of approximately 27 months.

3.5.2. ZA Substudy Treatment

Subjects that completed their OLP denosumab visit are eligible to participate in the ZA substudy as long as all the substudy inclusion/exclusion criteria are met.

Zoledronic acid will be administered 8 months (± 4 weeks) after last OLP administration for subjects randomized to treatment arm. Subjects randomized to SOC, will attend the site for visits at the same visit schedule as the treatment arm subjects.

Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit.

[redacted]

3.5.3. End of ZA Substudy

The end of ZA substudy will occur when the last subject participating in the ZA substudy has completed their last formal visit or an unscheduled study visit in case of early withdrawal from the ZA substudy.

End of study reasons include 3 early EOS reasons (death, lost to follow-up, and consent withdrawal) and per protocol EOS of ZA substudy.

4. ELIGIBILITY CRITERIA

4.5. Inclusion Criteria for ZA Substudy

4.5.1. Obtain signed and dated written informed consent prior to performing any substudy-specific procedure

4.5.2. Subjects that received OLP denosumab and completed OLP treatment

4.5.3. Last OLP denosumab administration no longer than 9 months ago

4.6. Exclusion Criteria for ZA Substudy

4.6.1. Current or prior ZA administration.

4.6.2. Subjects who ended treatment with investigational product (IP) prematurely in the double-blind phase and OL phase

4.6.3. Known sensitivity or intolerance to any of the products to be administered during the substudy (eg, ZA, calcium or vitamin D)

4.6.4. Known history of any of the following conditions either by subject self report or chart review

- Paget's disease (bone), Cushing's disease, hyperprolactinemia or other active metabolic bone disease
- Known history of hypocalcemia
- Major surgery, or significant traumatic injury occurring within 4 weeks prior to randomization
- Parathyroid glands in neck surgically removed.
- Any sections of intestine removed.
- Known human immunodeficiency virus infection
- Active infection with hepatitis B or hepatitis C virus

4.6.5. Known liver or renal disease as determined by the investigator and indicated by the following criteria:

- Aspartate aminotransferase ≥ 2.5 x ULN
- Alanine transaminase ≥ 2.5 x ULN
- Serum creatinine ≥ 2 x ULN
- Creatine clearance < 35ml/min

4.6.6. Subjects that are pregnant or breastfeeding

- All subjects with reproductive potential must have a negative pregnancy test within 7 days before randomization

4.6.7. Subjects who are osteoporotic in baseline BMD

5. SUBJECT ENROLLMENT

A subject will be assigned by an Interactive Voice/Web Response System to 1 of 2 treatment groups (ZA or SOC), in a 1:1 ratio. The randomization schedule will use randomly permuted blocks and will be stratified by AI use at the timepoint of OLP denosumab completion (Yes or No). A subject who is randomized to the ZA substudy will maintain the same subject number which is also the subject number as assigned in the double-blind (main) study. A subject may only be randomized once into ZA substudy. The ZA randomization list will be generated and maintained by an Amgen representative not involved in the conduct of the study.

6. TREATMENT PROCEDURES

6.1. Investigational Product (Zoledronic Acid) Dosage, Administration, and Schedule

Subjects will be randomized 1:1 to receive a single 5 mg IV of ZA or SOC 8 months (± 4 weeks) after completing OLP.

For those subjects randomized to receive ZA, this will be administered slowly as a constant infusion rate. The infusion time must not be less than 15 minutes, after all other study visit procedures have been completed.

Zoledronic Acid must only be prescribed and administered to subjects by healthcare professionals experienced in the administration of IV bisphosphonates. Subjects treated with ZA should be given the package leaflet. ZA will be locally provided by participating sites and will be reimbursed by the sponsor.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.Refer to the summary of product characteristics (SmPC) (https://www.ema.europa.eu/en/medicines/human/EPAR/zometa#product-information-section) for detailed information on the administration of ZA.

6.2. Prohibited medications

There are no prohibited medications in the ZA substudy.

7. STUDY PROCEDURES

[redacted]

7.4. Laboratory Assessments

As described in eligibility criteria for this substudy, routine laboratory assessments (at least for ALT, AST, serum creatinine, creatine clearance and calcium) to determine eligibility must be performed before randomization. Patients with child bearing potential must have a negative pregnancy test within 7 days prior to randomization. Subjects who have undergone a hysterectomy do not require a pregnancy test.

[redacted]

8. ADVERSE EVENT REPORTING

During the substudy, all SAEs and AEs of special interest (renal toxicity, clinically relevant hyper/hypocalcemia, and oral events) will be documented from signing the ICF for the ZA substudy until the last study visit (18 months after Day 1) in the Adverse Event eCRF.

For subjects participating in the substudy, the investigator is responsible for ensuring all SAEs observed by the investigator or reported by the subject that occur after signing of the ICF for the ZA substudy until the last study visit (18 months after Day 1), are recorded in the subjects medical record, the Adverse Event eCRF, and are submitted to Amgen.

New clinical fractures will be collected and any suspected atypical femoral fracture (femur midshaft fracture, femur subtrochanteric, or femur distal) associated with minimal trauma will be classified as an SAE for all subjects (see Section 9.1.2), and should be recorded in the subject's medical record, applicable fracture-recording CRF, and on a Serious Adverse Event Report form (see Appendix F) then faxed to the local Amgen Safety Specialist within 24 hours of discovery or notification of the event (see Section 9.3).

SAE reporting period for suspected atypical femoral fracture will be until EOS.

9. STATISTICAL CONSIDERATIONS

9.1. Exploratory Endpoints

[redacted]

9.2. Subsets

[redacted]

9.3. Sample Size Considerations

For the ZA substudy, it is anticipated that approximately 200 subjects could be randomized.

Data is limited on BMD for subjects who discontinue denosumab 60 mg Q6M in the oncology setting. Therefore, data from postmenopausal osteoporosis was used in the sample size.

A phase 2 randomized blinded clinical trial in postmenopausal women with low bone mass assessed the effect of denosumab 60 mg Q6M on BMD and bone turnover markers (CTX and Osteocalcin) after long-term continued, discontinued, and restarting of therapy (Miller et al, 2008). One of the treatment cohorts received denosumab 210 mg Q6M for 24 months then placebo for the next 24 months. Based on this study, a 5% (SD = 4.3%), 5.2% (SD = 2.6%), and 3.9% (SD = 3.8%) decrease in the lumbar spine, total hip, and femoral neck BMD was seen during the 2 years after denosumab discontinuation (data on file).

A paper reporting 22 case studies of postmenopausal women who received 5 injections (approximately 2.5 years) of denosumab 60 mg Q6M and were then given a single dose of ZA 6 months after the fifth injection (Lehmann and Aeberli, 2017). A 3.8% (SD = 2.8%), 1.7% (SD = 3.3%), and 0.6% (SD = 5%) decrease in the lumbar spine, total hip, and femoral neck BMD was seen during the 2.5 years after denosumab discontinuation.

A table showing the level of precision (ie, half width of 95% CI) for each treatment arm and each BMD type for different sample sizes, calculated based on the standard deviations estimated from the 2 studies mentioned above, is presented below.

Table 3. Sample Sizes

Number of subjects in each arm	Precision (half width of 95% confidence interval)					
	Standard of care			IV zoledronic acid		
	Lumbar Spine	Total Hip	Femoral Neck	Lumbar Spine	Total Hip	Femoral Neck
75	± 1.0%	± 0.6%	± 0.9%	± 0.6%	± 0.8%	± 1.1%
100	± 0.9%	± 0.5%	± 0.7%	± 0.5%	± 0.7%	± 1.0%
125	± 0.8%	± 0.5%	± 0.7%	± 0.5%	± 0.6%	± 0.9%

IV = intravenous

9.4. Access to Individual Subject Treatment Assignments

Subjects in ZA substudy will be randomized 1:1 to receive single dose ZA 5 mg IV (investigational product) or SOC.

9.5. Timepoint of Analysis

[redacted]

9.6. Planned Methods of Analysis

[redacted]

10. REFERENCES

Hadji P, Aapro MS, Body JJ, Gnant M, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. *J Bone Oncol.* 2017; 23;7:1-12.

Lehmann T, Aeberli D. Possible protective effect of switching from denosumab to zoledronic acid on vertebral fractures. *Osteoporos Int.* 2017;28(10):3067-3068.

Miller PD, Bolognese MS, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinding phase 2 clinical trial. *Bone.* 2008;43(2):222-229.

11. SCHEDULE OF ASSESSMENTS

Table 4. Schedule of Assessments for ZA Substudy

Study assessment	Screening/baseline	Randomization	Q6M Visit	Q12M Visit	Q18M Visit = EOS[a]
Re-consent	X				
Randomization		X			
IV Zoledronic acid (5mg x 1)[b]		X			
[redacted]					
Laboratory Assessment[e]	X				
[redacted]					

[redacted] EOS= end of study; IV = intravenous; M = month; OL = open-label; OLP = open-label phase; QXM= every X months; [redacted] SOC = standard of care; ZA = zoledronic acid.

The screening phase starts from date of the last OLP denosumab administration at the earliest and lasts until randomization but must occur afterwritten consent has been obtained.

Written consent may be obtained from date of the last OLP denosumab administration until 9 months after.

Randomization can be performed within 8 days prior to Day 1.

Visits to site: Day 1 after re-consent and randomization, 6, 12, and 18 months (± 2 weeks) after day 1.

[a] EOS: End of ZA substudy will be 18 months after day 1; or the last scheduled visit in case patient ends study prematurely.

[b] ZA administration must take place within 8 days after randomization. Half of the patients will be randomized to SOC (No ZA). Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit. Visits will take place 6, 12, 18 months after day 1.S

[redacted]

[e] Routine laboratory at least for ALT, AST, serum creatinine, creatine clearance and calcium assessments to determine eligibility must be performed before randomization. A negative pregnancy test within 7 days prior to randomization has to be available for women of childbearing potential. Subjects who have undergone a hysterectomy do not require a pregnancy test

[redacted]

12. PHARMACY GUIDE FOR ZA SUBSTUDY

ZA Substudy Investigational Product (Zoledronic Acid) Dosage, Administration, and Schedule

Subjects will be randomized 1:1 to receive a single 5 mg IV of ZA or SOC 8 months (± 4 weeks) after completing OLP.

For those subjects randomized to receive ZA, this will be administered slowly as a constant infusion rate. The infusion time must not be less than 15 minutes, after all other study visit procedures have been completed.

Zoledronic Acid must only be prescribed and administered to subjects by healthcare professionals experienced in the administration of IV bisphosphonates. Subjects treated with ZA should be given the package leaflet. ZA will be locally provided by participating sites and will be reimbursed by the sponsor.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Amendment 6 (added ZA substudy)

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study to Determine the Treatment Effect of Denosumab in Subjects With Non-Metastatic Breast Cancer Receiving Aromatase Inhibitor Therapy

Amgen Protocol Number 20050209

ABCSG Protocol Number ABCSG 18

EudraCT Number 2005-005275-15

NCT00556374

Amendment 5 Date:	01 April 2019
Amendment 6 Date:	15 July 2019

Rationale for Amendment 5 and 6:

Protocol amendment 5 dated 01 April 2019 was done to add an optional investigation of additional zoledronic acid (ZA) after completing open-label denosumab to the main body of the protocol. After their review, the lead ethics committee advised that this research question of additional ZA administration should rather be structured and submitted as a substudy. As sites have not seen protocol amendment 5, both changes for protocol amendment 5 and protocol amendment 6 are presented below.

Rationale for Amendment 5:

This protocol is being amended to:

- Add a randomization on patients still on open label denosumab to be treated with either a bisphosphonate or standard of care upon denosumab discontinuation
- Add exploratory objective to [redacted]

- Update the timing of ZA dose to 8 months (± 4 weeks) from the last dose of open-label denosumab because this is the moment where there is increase in the bone turnover marker, CTX, making it then the optimal moment for ZA to act
- Clarify that C-terminal telopeptide data will be collected during post open-label denosumab extension at specified times
- Clarify time periods for assessment during the extension to the open-label phase.
- Clarify analysis of the endpoints following the post open-label denosumab extension
- Add schema describing post open-label denosumab discontinuation extension
- Specify the approximate number of study sites in Austria participating in the post open-label denosumab extension
- Specify the approximate number of subjects participating in the post open-label denosumab extension
- Add a maximum of approximately 18 months to the study duration
- Add inclusion and exclusion criteria for post open-label denosumab zoledronic acid extension
- Add exclusion criteria for double-blind phase of the study
- Extend the expected time on study
- Clarify the End of Study definition
- Clarify that during the post open-label denosumab extension, no investigational product will be provided
- Make editorial and administrative changes for grammatical reasons as well as for internal consistency within the protocol.

Rationale for Amendment 6:

- Description of ZA substudy was removed from the body of the protocol and added to Appendix G.

Description of Changes for Protocol Amendment 5:

Section: Global

Change: The Amgen global version date was changed from 22 February 2016 to 01 April 2019.

Section: Global

Change: Editorial, typographical, and formatting changes were made throughout the document.

Section: Title Page

Add:

Amgen Protocol Number 20050209
ABCSG Protocol Number ABCSG 18
EudraCT #: 2005-005275-15
NCT00556374

Section: Title Page

Replace:

Key Sponsor Contact:	[redacted] Clinical Research Study Manager Amgen Limited United Kingdom Phone: [redacted] email:

With:

Key Sponsor Contact:	[redacted] **Global Clinical Trial Manager** Amgen Limited United Kingdom Phone: [redacted] **E**mail:

Section: Title Page

Add:

Date:	**01 April 2019 Amendment 5**

Section: Protocol Synopsis (Exploratory Objectives), Bullet point 3

Add:

[redacted]

Section: Protocol Synopsis (Study Design), Paragraphs 14 and 17 through 25

Add:

In addition, for all subjects, BMD data will be collected at any time a DXA scan is performed for BMD analysis as standard of care **(SOC)** from PADCD to end of study **(EOS)**; these data will be collected in the CRF.

At the end of the **main** study **(LTFU and OLP)**, a final analysis will occur looking at the secondary disease outcome-related endpoints (OS and BMFS) as well as an exploratory analysis of [redacted]. **Data collected during the post OL denosumab extension will be censored at the End of Open-label Treatment Visit or the EOS Visit (LTFU and OLP), whichever occurs later, for the final analysis.**

Post Open-label Denosumab Zoledronic Acid Extension (ZA extension):

Denosumab cessation is associated with a decline in bone mass that approach pre-treatment levels and available data suggest an increase in multiple vertebral fractures after discontinuation. Bisphosphonate treatment after denosumab may be warranted to potentially prevent these fractures, particularly in patients not previously exposed to bisphosphonates and who remain at high fracture risk (ie, osteoporosis with previous vertebral fractures), but limited data is available confirming the validity of this hypothesis. Therefore, there is a data gap regarding optimal strategies for patients who will discontinue denosumab and this protocol amendment is designed to help address that question.

After regulatory and IRB/IEC approval of Protocol Amendment 5, willing and eligible subjects who participated in the OLP of the study and completed OL denosumab may opt in this ZA extension and either receive a single dose of ZA (Therapy Arm), or are managed according to the current SOC for this patient population (Control Arm). Patients who completed OLP denosumab and ended study as defined per protocol are eligible to participate in the ZA extension trial as long as the outlined criteria are fulfilled. Written consent may be obtained from

date of the last OLP denosumab administration until 9 months after. The screening phase starts from date of the last OLP denosumab administration at the earliest and lasts until randomization, but must occur after written consent has been obtained.

Willing and eligible subjects who completed OL denosumab are randomized to 1 single 5 mg IV dose of ZA or to SOC. Randomization can be performed within 8 days prior to Day 1. Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit. Follow up will continue for a total of 18 months after day 1. Randomization will be stratified by AI use at the timepoint of OLP denosumab completion (Yes or No).

DXA scan can be performed between 7 to 9 months after the date of the last denosumab administration, but in any case before the date of first ZA administration. Routine DXA scans performed within the outlined time window can be used as baseline DXA scans.

Subjects who do not fulfill the eligibility criteria for or do not consent to the ZA extension will complete OLP assessments only.

Subjects who participate in the ZA extension, will undergo the following assessments:

[redacted]

Section: Protocol Synopsis (Exploratory Endpoints)

Add:

Exploratory Endpoints:

Subjects who participate in the ZA extension:

[redacted]

Section: Protocol Synopsis (Summary of Subject Eligibility Criteria)

Add:

Summary of Subject Eligibility Criteria **(Double-blind Phase)**

Section: Protocol Synopsis (Exclusion Criteria)

Add:

Subjects completing OL denosumab may be eligible for the ZA extension.

Section: Protocol Synopsis (Investigational Product Dosage and Administration in double-blind phase and in the OLP)

Add:

Investigational Product Dosage and Administration in Double-blind Phase and in the OLP:

Section: Protocol Synopsis (Investigational Product Dosage and Administration in ZA Extension)

Add:

Investigational Product Dosage and Administration in ZA Extension:

Therapy Arm: ZA 5 mg IV single dose

Control Arm: SOC

Section: Protocol Synopsis (Long-term Follow-up), Paragraph 6

Add:

Post Open-label Denosumab Extension (ZA extension):

[redacted]

Section: Protocol Synopsis (Statistical Considerations), Paragraph 4 and 7

Add:

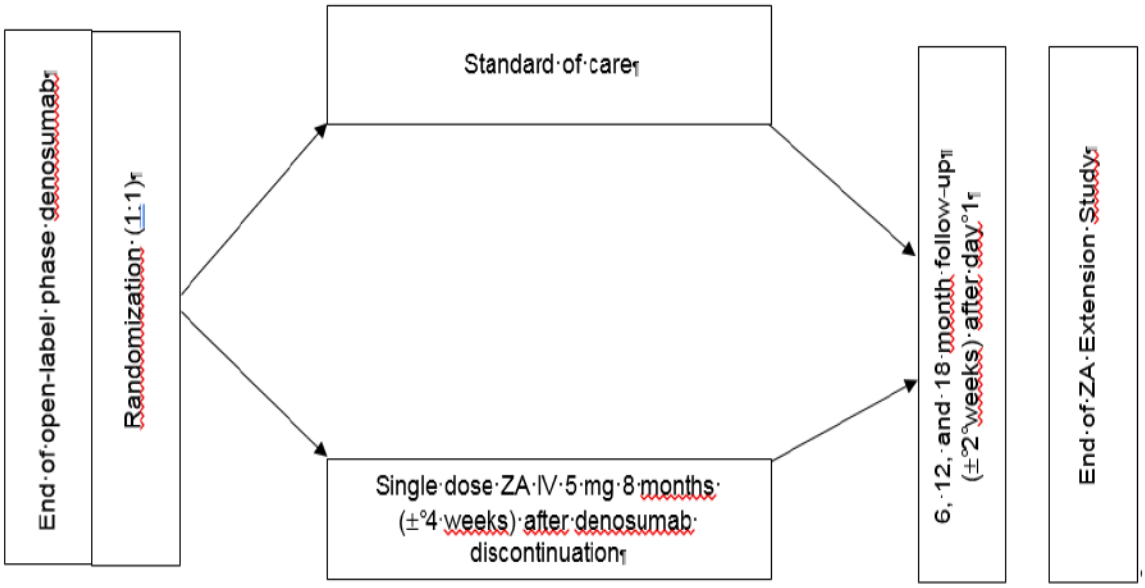
At the end of the **main** study **(LTFU and OLP)**, a final analysis will occur looking at the secondary disease outcome-related endpoints (OS and BMFS) as well as an exploratory analysis of [redacted] **for the main study**. [redacted] **Only data collected up to the EOS visit (end of OL treatment visit or their last scheduled LTFU visit) will be included in the final analysis. Any data collected for the post OL denosumab extension will be excluded.**

Analysis of the endpoints from the ZA Extension will be descriptive only and will take place when all subjects randomized to the extension have attended their last study visit. The analyses will be performed after the final analysis of fracture-related and disease-related outcomes for the main study.

Section: Study schema, Post Open-label Denosumab ZA Extension Study Design and Treatment Schema

Add:

Post Open-label Denosumab ZA Extension Study Design and Treatment Schema



IV = intravenous; ZA = zoledronic acid.

Section: Study Glossary

Add:

Abbreviation/Acronym/Study term	Definition
CTX	**C-terminal telopeptide**
Day 1 **in double-blind phase and OLP**	first day investigational product is administered
Day 1 in ZA extension	**Defined as 8 months (± 4 weeks) after the last OLP denosumab dose** **For treatment arm: first day ZA is administered** **For control arm (SOC treatment): SOC day 1 visit**
End of Open-Label Treatment Visit	the last assessment of the protocol specified open-label treatment for a subject. **If not eligible for post OL denosumab ZA extension or willing to take part in this study, subjects will complete an end of OL treatment visit 30 to 45 days after the last dose of OL denosumab either by clinic visit or telephone contact.**
End of Study (EOS) of ZA Extension	**The date when the last subject participating in the ZA Extension completes the last formal visit or an unscheduled study visit in case of early withdrawal from the ZA extension**
End of Treatment **in double-blind phase**	last administration of double-blind investigational product for each subject
End of Treatment visit **in double-blind phase**	the visit at which the subject receives the last dose of IP; for all subjects, whose last regular study visit within 6 months (+ 45 days time window) prior to the PADCD was a yearly visit (eg, months 12, 24, etc) and radiological assessments were performed, this visit will be considered an EOT visit. Those subjects, for whom the radiological assessments were not performed, will need to attend the next scheduled 6 months visit, when radiological assessments (vertebral x-rays, DXA) will take place and an antibody sample will be taken. For these subjects this visit will be considered as EOT visit. For those whose last regular study visit within 6 months (+ 45 days time window) prior to the PADCD was a 6 months visit (eg, month 6, 18, etc), the next regularly scheduled yearly study visit (eg, Q12M) within 6 months after PADCD will be considered an EOT visit
Final analysis	analysis performed after long-term follow up, **and OLP,** approximately 66 months after PADCD, depending on the interim analysis
M	**month(s)**
OL	**open-label**
SmPC	**summary of product characteristics**
SOC	**standard of care**
ZA	**zoledronic acid**
ZA Extension Treatment	**Subject randomized to treatment arm will receive a single dose ZA.**

Section: 1.3 Exploratory, Bullet point 3

Add:

[redacted]

Section: 2.3 Rationale, Paragraph 11

Add:

BMD Changes After Open-label Denosumab Zoledronic Acid Extension (ZA Extension):

Denosumab cessation is associated with declines in bone mass that approach pre-treatment levels and available data do suggest an increase in multiple vertebral fractures after discontinuation. Bisphosphonate treatment after denosumab may be warranted to potentially prevent these fractures, particularly in patients not previously exposed to bisphosphonates and who remain at high fracture risk (ie, osteoporosis with previous vertebral fractures), but limited data are available confirming the validity of this hypothesis. Therefore, there is a data gap regarding optimal strategies for patients who will discontinue denosumab. The ABCSG18 Post Open-label Denosumab Extension (ZA Extension) is designed to evaluate on patients discontinuing denosumab, to either receive a single dose of ZA, or to be managed according to current standard of care (SOC) for respective patient population after denosumab discontinuation.

Section: 3.1 Study Design (Open-label Phase), Paragraph 4, Bullet 2

Add:

- Collection of serious and non-serious **adverse events** [(S)AEs] of special interest (oral events) and SAEs

Section: 3.1 Study Design (Post Open-label Denosumab Zoledronic Acid Extension [ZA Extension])

Add:

Post Open-label Denosumab Zoledronic Acid Extension (ZA Extension):

[redacted]

After regulatory and IRB/IEC approval of Protocol Amendment 5, willing and eligible subjects who participated in the OLP of the study and completed OL denosumab may opt in this ZA extension and either receive a single dose of ZA (Therapy Arm), or are managed according to the current SOC for this patient population (Control Arm). Patients who completed OLP denosumab and ended study as defined per protocol are eligible to participate in the ZA extension trial as long as the outlined criteria are fulfilled.

Written consent may be obtained from date of the last OLP denosumab administration until 9 months after. The screening phase starts from date of the last OLP denosumab administration at the earliest and lasts until randomization, but must occur after written consent has been obtained.

Willing and eligible subjects who completed OL denosumab are randomized to 1 single 5 mg IV dose of ZA or to SOC. Randomization can be performed within 8 days prior to Day 1. Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit. Follow up will continue for a total of 18 months after day 1. Randomization will be stratified by AI use at the timepoint of OLP denosumab completion (Yes or No).

DXA scan can be performed between 7 to 9 months after the date of the last denosumab administration, but in any case before the date of first ZA administration. Routine DXA scans performed within the outlined time window can be used as baseline DXA scans.

Subjects who do not fulfill the eligibility criteria for or do not consent to the ZA extension will complete OLP assessments only.

Subjects who participate in the ZA extension, will undergo the following assessments:

[redacted]

Section: 3.1 Study Design, Duble-blind Phase, Paragraph 2

Delete:

For a subject with > 10% loss of BMD at the total hip or lumbar spine over any 1-year period, an informed discussion will take place between the investigator and the subject regarding alternative therapies and appropriate treatment. If the selected treatment option does not include commercially available denosumab (ie, XGEVA® or Prolia®), ~~intravenous (~~IV~~)~~ bisphosphonates or orally administered bisphosphonate therapy lasting longer than 30 days, which is exclusionary (leading to early EOT), the subject will remain in the study.

Section: 3.2 Number of Centers, Paragraph 2

Add:

Approximately 30 sites in Austria are anticipated to participate in the ZA extension.

Section: 3.3 Number of Subjects, Paragraph 3

Add:

Approximately 200 subjects are anticipated to participate in the ZA extension.

Section: 3.4 Estimated Study Duration

Add:

The actual timing of analyses will be determined by the PADCD. Study duration is estimated to be 169 months, which includes an enrollment period of approximately 82 months, an end of the treatment phase (ie, the PADCD) of approximately 21 months and approximately 66 months following the PADCD for a 5 year long-term follow-up including an OLP (12 months unblinding option and a maximum of 36 months of treatment) (.see Sections 7.15 and 10.5). **Amendment 5 (ZA extension) will add a maximum of approximately 27 months (considering that the patient may enter the extension study 9 months after OLP denosumab completion) to the study duration.**

Section: 3.4.1 Study Duration for Participants, Paragraphs 2 and 3

Replace:

Subjects who receive open-label denosumab will be followed-up until completion of 36 months of treatment or approximately 66 months after PADCD, whichever is longer. The expected time on study is up to approximately 169 months.

With:

Subjects who receive open-label denosumab will be followed-up until completion of 36 months of treatment or approximately 66 months after PADCD, whichever is longer. **Subjects in the OLP may consent to an extension to assess discontinuation from denosumab and receive either single dose ZA 5 mg IV or SOC treatment, which will be for a maximum duration of approximately 27 further months.**
The expected time on study is up to approximately **196** months.

Section: 3.4.3 Long-term Follow-up, Paragraph 1

Replace:

Subjects will be followed for DFS, BMFS, and OS Q12M by clinic visits or telephone contacts starting from their last study visit (considered as EOS visit) for approximately 66 months after the PADCD (see Sections 7.15 and 10.5). Following regulatory and

IRB/IEC approval of Protocol Amendment 4, further data will be assessed (see Section 3.1).

With:

Subjects will be followed for DFS, BMFS, and OS Q12M by clinic visits or telephone contacts starting from their last study visit (considered as **EOT** visit) for approximately 66 months after the PADCD (see Sections 7.15 and 10.5). Following regulatory and IRB/IEC approval of Protocol Amendment 4, further data will be assessed (see Section 3.1).

Section: 3.4.5 Post Open-label Denosumab ZA Extension Treatment (New Section)

Add:

3.4.5 Post Open-label Denosumab ZA Extension Treatment

Patients that completed their OLP denosumab visit and ended the study as defined per protocol are eligible to participate in the ZA extension as long as all inclusion/exclusion criteria are met.

Zoledronic acid will be administered 8 months (± 4 weeks) after last OLP administration for subjects randomized to treatment arm. Subjects randomized to SOC, will attend the site for visits at the same visit schedule as the treatment arm subjects.

Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit.

[redacted]

Section: 3.4.6 End of Study (Double-blind Phase and OLP), Paragraph 1

Replace:

3.4.6 End of Study

The end of the study will occur when the last subject has completed their last formal visit or last formal contact or an unscheduled study visit in case of early withdrawal from the study. This is expected to occur when the last subject completes their end of open-label treatment visit or their last scheduled LTFU visit.

With:

3.4.6 End of Study **(Double-blind Phase and OLP)**

The end of the study will occur when the last subject has completed their last formal visit or last formal contact or an unscheduled study visit in case of early withdrawal from the study. This is expected to occur when the last subject completes **the extension to the OL treatment period** or their last scheduled LTFU visit.

Section: 3.4.7 End of Study of ZA Extension (New Section)

Add:

3.4.7 End of Study of ZA Extension

The end of ZA Extension will occur when the last subject participating in the ZA Extension has completed their last formal visit or an unscheduled study visit in case of early withdrawal from the ZA extension.

End of study reasons include 3 early EOS reasons (death, lost to follow-up, and consent withdrawal) and per protocol EOS of ZA Extension.

Section: 4.2 Exclusion Criteria for Double-blind Phase, Exclusion criteria 4.2.7, bullet 1

Replace:

4.2.7 Known liver or renal disease as determined by the investigator and indicated by the following criteria:

- Asparate aminotransferase ≥ 2.5 x upper limit of normal (ULN)

With:

4.2.7 Known liver or renal disease as determined by the investigator and indicated by the following criteria:

- **Aspartate** aminotransferase ≥ 2.5 x upper limit of normal (ULN)

Section: 4.5 Inclusion Criteria for Post Open-label Denosumab Zoledronic Acid Extension (ZA Extension) (New Section)

Add:

4.5 Inclusion Criteria for Post Open-label Denosumab Zoledronic Acid Extension (ZA Extension)

4.5.1 Obtain signed and dated written informed consent prior to performing any study-specific procedure

4.5.2 Subjects that received OLP denosumab and completed OLP treatment

4.5.3 Last OLP denosumab administration no longer than 9 months ago

Section: 4.6 Exclusion Criteria for Post Open-label Denosumab Zoledronic Acid Extension (New Section)

Add:

4.6 Exclusion Criteria for Post Open-label Denosumab Zoledronic Acid Extension

4.6.1 Current or prior ZA administration.

4.6.2 Subjects who ended treatment with investigational product (IP) prematurely in the double-blind phase and OL phase

4.6.3 Known sensitivity or intolerance to any of the products to be administered during the study (eg, ZA, calcium or vitamin D)

4.6.4 Known history of any of the following conditions either by subject self report or chart review

- **Paget's disease (bone), Cushing's disease, hyperprolactinemia or other active metabolic bone disease**
- **Known history of hypocalcemia**
- **Major surgery, or significant traumatic injury occurring within 4 weeks prior to randomization**
- **Parathyroid glands in neck surgically removed**
- **Any sections of intestine removed**
- **Known human immunodeficiency virus infection**
- **Active infection with hepatitis B or hepatitis C virus**

4.6.5 Known liver or renal disease as determined by the investigator and indicated by the following criteria:

- **Aspartate aminotransferase ≥ 2.5 x ULN**
- **Alanine transaminase ≥ 2.5 x ULN**
- **Serum creatinine ≥ 2 x ULN**
- **Creatine clearance < 35ml/min**

4.6.6 Subjects that are pregnant or breastfeeding

- **All subjects with reproductive potential must have a negative pregnancy test within 7 days before randomization**

4.6.7 Subjects who are osteoporotic in baseline BMD

Section: 5.6 Post Open-label Denosumab ZA Extension (New section)

Add:

5.6 Post Open-label Denosumab ZA Extension

A subject will be assigned by an Interactive Voice/Web Response System to 1 of 2 treatment groups (ZA or SOC), in a 1:1 ratio. The randomization schedule will use randomly permuted blocks and will be stratified by AI use at the timepoint of OLP denosumab completion (Yes or No). A subject who is randomized to the ZA Extension will maintain the same subject number which is also the subject number as assigned in the double-blind study. A subject may only be randomized once into ZA Extension. The ZA randomization list will be generated and maintained by an Amgen representative not involved in the conduct of the study.

Section: 6.3 Prohibited Medication in Post Open-label Denosumab ZA Extension (New section)

Add:

6.3 Prohibited Medication in Post Open-label Denosumab ZA Extension

Subjects participating in the ZA Extension will follow the same visit schedule as outlined in the ZA Extension (Appendix A, Schedule of Assessments). There are no prohibited medications in this extension.

6.3.1 Investigational Product (Denosumab)

No denosumab is required or provided for patients in the post OL denosumab extension.

6.3.2 Non Investigational Product Dosage, Administration, and Schedule

Subjects will be randomized 1:1 to receive a single 5 mg IV of ZA or SOC 8 months (± 4 weeks) after completing OLP.

For those subjects randomized to receive ZA, this will be administered slowly as a constant infusion rate. The infusion time must not be less than 15 minutes, after all other study visit procedures have been completed.

Zoledronic Acid must only be prescribed and administered to patients by healthcare professionals experienced in the administration of IV bisphosphonates. Patients treated with ZA should be given the package leaflet.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Refer to the summary of product characteristics (SmPC) (https://www.medicines.org.uk/emc/product/44/smpc) for detailed information on the administration of ZA.

6.3.3 Prohibited medications

There are no prohibited medications in the post OL denosumab extension.

Section: 7.7.1 Assessment of Clinical Fractures During Open-label Phase, Subtitle

Add:

7.7.1 Assessment of Clinical Fractures During Open-label Phase **and ZA Extension**

[redacted]

Add:

[redacted]

Section: [redacted]

Add:

[redacted]

Section: 7.13 Laboratory Assessments in ZA Study (New Section)

Add:

7.13 Laboratory Assessments in ZA Study

Routine laboratory assessments to determine eligibility must be performed before randomization. Patients with child bearing potential must have a negative pregnancy test within 7 days prior to randomization. Subjects who have undergone a hysterectomy do not require a pregnancy test.

Section: 7.14.1 Blood and Serum Assessments in ZA Extension (New Section)

Add:

[redacted]

Table 1. Serum and Blood Sample Analyte Listing

Serum Chemistry	Hematology	Other
Sodium	Red blood cells	Denosumab antibody assay **(only double-blind study)**
Potassium	Hemoglobin	[redacted]
Calcium	Hematocrit	
Blood Urea Nitrogen/Urea	Platelets	
Creatinine	White blood cells	
Total bilirubin		
Alkaline phosphatase		
Alanine transaminase		
Asparate aminotransferase		
LDH		
Gamma GT		
Albumin		

[redacted]

[redacted]

Section: 7.15 Adverse Events, Open-label Phase/Long-term Follow-up, Paragraphs 3 and 4

Add:

Post Open-label Denosumab Zoledronic Acid Extension (ZA Extension):

During the post OL denosumab extension, (S)AEs of special interest (causal relationship to ZA and oral events) will be documented for subjects receiving ZA.

New clinical fractures will be collected and any suspected atypical femoral fracture (femur midshaft fracture, femur subtrochanteric, or femur distal) associated with minimal trauma will be classified as an SAE for all subjects (see Section 9.1.2), and should be recorded on a Serious Adverse Event Report form (see Appendix F) and faxed to the local Amgen Safety Specialist within 24 hours of discovery or notification of the event (see Section 9.3).

Section: 7.20 Post Open-label Denosumab Extension (New Section)

Add:

7.20 Post OL Denosumab Zoledronic Acid Extension (ZA Extension)

Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit.

Follow up will continue for a total of 18 months after day 1.

Section: 7.21 End of Study, Paragraph 1

Add:

The **patient individual** EOS is defined as the last formal visit or contact for a subject or an unscheduled study visit in case of early withdrawal from study. **The overall EOS will occur when the last subject has completed their last formal visit or last formal contact or an unscheduled study visit in case of early withdrawal from the study.** This is expected to occur when the last subject completes their end of open-label treatment visit or their last scheduled LTFU visit.

Section: 7.22 End of Study of ZA Extension (New Section)

Add:

7.22 End of Study of ZA Extension

The end of ZA extension will occur when the last subject participating in the ZA extension has completed their last formal visit or an unscheduled study visit in case of early withdrawal from the ZA extension.

End of ZA extension study will be 18 months after day 1.

End of study reasons include 3 early EOS reasons (death, lost to follow-up, consent withdrawal) and per protocol EOS of ZA extension.

Section: 9.3.1, Adverse Events of Special Interest and Serious Adverse Event Reporting During the Open-label Phase (Section Title)

Add:

9.3.1 Adverse Events of Special Interest and Serious Adverse Event Reporting During the Open-label Phase **and Post Open-label Denosumab Extension**

Section: 9.3.1.2, Serious Adverse Event Reporting, Paragraphs 3 and 4

Add:

For subjects participating in the post OL denosumab extension and receiving ZA, the investigator is responsible for ensuring all SAEs observed by the investigator or reported by the subject that occur after signing the ICF for the extension until the last study visit (18 months after Day 1), are recorded in the subjects medical record and are submitted to Amgen. New clinical fractures will be collected and any suspected atypical femoral fracture (femur midshaft fracture, femur subtrochanteric, or femur distal) associated with minimal trauma will be classified as an SAE for all subjects (see Section 9.1.2), and should be recorded on a Serious Adverse Event Report form (see Appendix F) and faxed to the local Amgen Safety Specialist within 24 hours of discovery or notification of the event (see Section 9.3).

In addition, any suspected atypical femoral fracture (femur midshaft fracture, femur subtrochanteric, or femur distal) associated with minimal trauma will be classified as an SAE for all subjects, and should be recorded in the subject's medical record and submitted to Amgen (see Appendix F- Clinical Trial Serious

Adverse Event report form) and recorded in the applicable fracture recording CRF. SAE reporting period for suspected atypical femoral fracture will be until EOS.

Section: 10.1 Study Design, Paragraph 2

Add:

[redacted]

Section: 10.2.4 Exploratory Endpoints, Subheading and bullets 6 through 8

Add:

Post Open-label Denosumab Extension (ZA extension):

[redacted]

Section: 10.2.5 Subsets, Paragraphs 2 and 3

Add:

[redacted]

The post denosumab OL safety analysis set will consist of all randomized subjects summarized under the actual treatment they received. Subjects who receive ZA will be summarized in the ZA arm while all other subjects will be summarized in the SOC arm. Serious adverse events associated with ZA

administration, [redacted]

Section: 10.3 Sample Size Considerations, Paragraphs 6 to 10

Add:

For the ZA extension, it is expected that approximately 200 subjects could be randomized.

Data is limited on BMD for subjects who discontinue denosumab 60 mg Q6M in the oncology setting. Therefore data from postmenopausal osteoporosis was used in the sample size.

A phase 2 randomized blinded clinical trial in postmenopausal women with low bone mass assessed the effect of denosumab 60 mg Q6M on BMD and bone turnover markers (CTX and Osteocalcin) after long-term continued, discontinued, and restarting of therapy (Miller et al, 2008). One of the treatment cohorts received denosumab 210 mg Q6M for 24 months then placebo for the next 24 months. Based on this study, a 5% (SD = 4.3%), 5.2% (SD = 2.6%), and 3.9% (SD = 3.8%) decrease in the lumbar spine, total hip, and femoral neck BMD was seen during the 2 years after denosumab discontinuation (data on file).

A paper reporting 22 case studies of postmenopausal women who received 5 injections (approximately 2.5 years) of denosumab 60 mg Q6M and were then given a single dose of ZA 6 months after the fifth injection (Lehmann and Aeberli, 2017). A 3.8% (SD = 2.8%), 1.7% (SD = 3.3%), and 0.6% (SD = 5%) decrease in the lumbar spine, total hip, and femoral neck BMD was seen during the 2.5 years after denosumab discontinuation.

A table showing the level of precision (ie, half width of 95% CI) for each treatment arm and each BMD type for different sample sizes, calculated based on the standard deviations estimated from the 2 studies mentioned above, is presented below.

Table 2. Sample Sizes

Number of subjects in each arm	Precision (half width of 95% confidence interval)					
	Standard of care			IV zoledronic acid		
	Lumbar Spine	Total Hip	Femoral Neck	Lumbar Spine	Total Hip	Femoral Neck
75	± 1.0%	± 0.6%	± 0.9%	± 0.6%	± 0.8%	± 1.1%
100	± 0.9%	± 0.5%	± 0.7%	± 0.5%	± 0.7%	± 1.0%
125	± 0.8%	± 0.5%	± 0.7%	± 0.5%	± 0.6%	± 0.9%

IV = intravenous

Section: 10.4 Access to Individual Subject Treatment Assignments, Paragraph 5

Add:

Eligible subjects who consent to the ZA extension do not receive any investigational product (denosumab), but will be randomized 1:1 to receive single dose ZA 5 mg IV or SOC.

Section: 10.5 Interim Analysis, Early Stopping Guidelines, and Time-points of Analyses, Paragraphs 5, 6, and 7

Add:

A final exploratory [redacted] analysis as well as the main analyses for efficacy of the secondary endpoints BMFS and OS will be performed at the end of the **main** study.

Additionally, [redacted] will be evaluated in a final exploratory analysis at this time point. **Only data collected up to the EOS visit (end of OL treatment visit or their last scheduled LTFU visit) will be included in the final analysis. Any data collected for the post OL denosumab extension will be excluded.**

[redacted] **Data collected during the ZA extension will be censored for this final analysis at the End of Open-Label Treatment Visit or the EOS Visit (LTFU and OLP), whichever occurs later.**

Section: 10.6.2.2 Safety Analyses, Paragraph 2

Replace:

The subject incidence rates of [redacted] reported during the OLP will be tabulated separately by system organ class and preferred term.

With:

The subject incidence rates of [redacted] reported during the OLP will be tabulated separately by system organ class and preferred term.

Section: 10.6.2.4 Exploratory Analyses, Paragraph 4

Add:

[redacted].

Section: 10.6.2.4 Exploratory Analyses, Pargraphs 7 through 10

Add:

[redacted]

[redacted]

Section: 11.1 Denosumab (Post Open-label Denosumab ZA Extension) (New subsection)

Add:

Post Open-label Denosumab ZA Extension:

No ZA will be provided for this extension.

Patients included in the treatment arm of the ZA extension will obtain ZA (IV 5 mg) via a prescription from their physician.

There are currently no guidelines or evidence regarding the best strategy to be considered when discontinuing denosumab in cancer treatment-induced bone loss. There has been expert opinion published stating that a transition to a bisphosphonate represents a treatment option (Hadji et al, 2017).

Section: 11.2.3 Post Open-label Denosumab ZA Extension (New section)

Add:

11.2.3 Post Open-label Denosumab ZA Extension

After the ICF is signed, randomization of subjects deemed eligible for the ZA Extension can occur, and ZA shall be administered 8 months (± 4 weeks) from the last dose of OL denosumab.

Patients included in the ZA arm of the post denosumab discontinuation OL administration will obtain ZA (IV 5 mg) via a prescription from their physician.

Refer to the SmPC (https://www.medicines.org.uk/emc/product/44/smpc) for detailed information on the administration of ZA.

Section: 12.4 Subject Confidentiality

Replace:

The investigator must ensure that the subject's confidentiality is maintained. On the case report forms or other documents submitted to Amgen/ABCSG, subjects should be identified by the subject study number only. Documents that are not for submission to

Amgen/ABSCG (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

With:

The investigator must ensure that the subject's confidentiality is maintained. On the case report forms or other documents submitted to Amgen/ABCSG, subjects should be identified by the subject study number only. Documents that are not for submission to Amgen/ABC**S**G (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

Section: 13.1 Protocol Amendments and Study Termination, Paragraph 1

Delete:

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 must be informed of all amendments and give approval. ABCSG must send a copy of the approval letter from the IEC to Amgen.

Section: 13.2 Study Documentation and Archive, Paragraph 1

Replace:

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.

With:

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 **ABCSG** Delegation of Authority Form.

Section: 13.2 Study Documentation and Archive, Paragraph 3, Bullet 1

Replace:

- Subject files containing completed case report forms, informed consent forms, and subject identification list.

With:

- Subject files containing completed informed consent forms and subject identification list. **Documentation of CRFs is visible via web-based electronic data capture (EDC) system at any time during the study. At database closure data will be provided on compact discs for filing purposes.**

Section: 13.3 Study Monitoring and Data Collection, Paragraph 5, 6, and 7

Replace:

Due to an unexpected change of the data management system, DATAPORT (software MACRO, provided by InferMED), has replaced "IntTrial®". The current system, DATAPORT, enables the investigator to work on a web-based online documentation (e-CRF).

MACRO provides communication tools which will help users to manage discrepancies electronically, to conduct source data verification and to improve communication within the study team.

- 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 ABCSG. 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 raised via EDC for site completion.
- The principal investigator will sign only the Investigator Verification Form and sign and date the indicated places on the CRF. These signatures will indicate that the principal investigator inspected or reviewed the CRF, the data queries, and the site notifications, and agrees with the content. Paper output of the CRF is available in case that the investigator or the IRB require hard copy output for review, signature, and storage at the end of the study.
- ABCSG's clinical data management department will ensure that the database is corrected for the following CRF issues without notification to site staff:
  - Formal corrections (eg, 12.01.2012 -> 12/01/2012, 1 per day -> 1/day)
  - misspellings that do not change the meaning of the word (excluding adverse events and medications)
  - location of data recorded on an incorrect CRF (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
  - administrative data (eg, event names for unscheduled visits or retests)
  - if both the end date and a status of continuing is indicated (eg, for adverse events, concomitant medication, hospitalization), the end date will supersede
  - If equivalent units or terms are recorded instead of the acceptable Amgen standard (eg, cc for mL, SQ for SC route, Not Examined for Not Done), the Amgen 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 CRF page numbers

A detailed description of further items for corrections without notification to site staff will be given in the Data Management Plan (DMP).

With:

Due to an unexpected change of the data management system, **the Interface** DATAPORT/**TRIALDATAPORT** (**EDC system** MACRO, provided by InferMED), has replaced "IntTrial®". The current **EDC system**, enables the investigator to work on a web-based online documentation (e-CRF).

MACRO provides communication tools which will help users to manage discrepancies electronically, to conduct source data verification and to improve communication within the study team.

- 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 ABCSG. 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 raised via EDC for site completion.
- The principal investigator will sign only the **Confirmation of Data Form**. These signatures will indicate that the principal investigator inspected or reviewed the CRF, the data queries, and the site notifications, and agrees with the content. Paper output of the CRF **can be printed out (tabular format) by the investigator whenever needed**.
- ABCSG's clinical data management department will ensure that the database is corrected for the following CRF issues without notification to site staff:
  - Formal corrections (eg, 12.01.2012 -> 12/01/2012, 1 per day -> 1/day)
  - misspellings that do not change the meaning of the word (excluding adverse events and medications)
  - location of data recorded on an incorrect CRF (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
  - administrative data (eg, event names for unscheduled visits or retests)
  - if both the end date and a status of continuing is indicated (eg, for adverse events, concomitant medication, hospitalization), the end date will supersede
  - If equivalent units or terms are recorded instead of the acceptable Amgen standard (eg, cc for mL, SQ for SC route, Not Examined for Not Done), the Amgen 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 CRF page numbers

A detailed description of further items for corrections without notification to site staff **is** given in the **respective** Data Management Plan (DMP).

Section: 14 References

Add:

Hadji P, Aapro MS, Body JJ, Gnant M, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. *J Bone Oncol.* 2017; 23;7:1-12.

Lehmann T, Aeberli D. Possible protective effect of switching from denosumab to zoledronic acid on vertebral fractures. *Osteoporos Int.* 2017;28(10):3067-3068.

Miller PD, Bolognese MS, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinding phase 2 clinical trial. *Bone.* 2008;43(2):222-229.

Section: 15 Appendix A, Schedule of Assessments for Denosumab Discontinuation Extension (New Table)

Add:

Schedule of Assessments for Post Open-label Denosumab Zoledronic Acid Extension (ZA Extension)

Study assessment	Screening/baseline	Randomization	Q6M Visit	Q12M Visit	Q18M Visit = EOS[a]
Re-consent	X				
Randomization		X			
IV Zoledronic acid (5mg x 1)[b]		X			
[redacted]					
Laboratory Assessment[e]	X				
[redacted]					

[redacted] EOS= end of study; IV = intravenous;
M = month;OL = open-label; OLP = open-label phase; QXM= every X months; [redacted] SOC = standard of care;
ZA = zoledronic acid..
The screening phase starts from date of the last OLP denosumab administration at the earliest and lasts until randomization but must occur after written consent has been obtained.
Written consent may be obtained from date of the last OLP denosumab administration until 9 months after.
Randomization can be performed within 8 days prior to Day 1.
Visits to site: Day 1 after re-consent and randomization, 6, 12, and 18 months (± 2 weeks) after day 1.

[a] EOS: End of ZA extension study will be 18 months after day 1; or the last scheduled visit in case patient ends study prematurely.
[b] ZA administration must take place within 8 days after randomization. Half of the patients will be randomized to SOC (No ZA). Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit. Visits will take place 6, 12, 18 months after day 1.

[redacted]

[e] Routine laboratory assessments to determine eligibility must be performed before randomization. A negative pregnancy test within 7 days prior to randomization. Subjects who have undergone a hysterectomy do not require a pregnancy test.

[redacted]

Description of Changes for Protocol Amendment 6 (added ZA substudy):

Section: Global

Change: The Amgen global version date was changed from 01 April 2019 to **15 July 2019.**

Section: Global

Replace:

Post OL denosumab extension

With:

ZA substudy

Section: Global

Replace:

ZA extension

With:

ZA substudy

Section: Global

Change: Editorial, typographical, and formatting changes were made throughout the document.

Section: Title Page

Add:

Date:	**15 July 2019 Amendment 6 (added zoledronic acid substudy)**

Section: Protocol Synopsis (Exploratory Objectives), Bullet point 3

Remove:

[redacted]

Section: Protocol Synopsis (Study Design)

Replace:

Post Open-label Denosumab Zoledronic Acid Extension (ZA extension):

Denosumab cessation is associated with a decline in bone mass that approach pre-treatment levels and available data suggest an increase in multiple vertebral fractures after discontinuation. Bisphosphonate treatment after denosumab may be warranted to potentially prevent these fractures, particularly in patients not previously exposed to bisphosphonates and who remain at high fracture risk (ie, osteoporosis with previous vertebral fractures), but limited data is available confirming the validity of this hypothesis. Therefore, there is a data gap regarding optimal strategies for patients who will discontinue denosumab and this protocol amendment is designed to help address that question.

After regulatory and IRB/IEC approval of Protocol Amendment 5, willing and eligible subjects who participated in the OLP of the study and completed OL denosumab may opt in this ZA extension and either receive a single dose of ZA (Therapy Arm), or are managed according to the current SOC for this patient population (Control Arm). Patients who completed OLP denosumab and ended study as defined per protocol are eligible to participate in the ZA extension trial as long as the outlined criteria are fulfilled. Written consent may be obtained from date of the last OLP denosumab administration until 9 months after. The screening phase starts from date of the last OLP denosumab administration at the earliest and lasts until randomization, but must occur after written consent has been obtained.

Willing and eligible subjects who completed OL denosumab are randomized to 1 single 5 mg IV dose of ZA or to SOC. Randomization can be performed within 8 days prior to Day 1. Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit. Follow up will continue for a total of 18 months after day 1. Randomization will be stratified by AI use at the timepoint of OLP denosumab completion (Yes or No).

DXA scan can be performed between 7 to 9 months after the date of the last denosumab administration, but in any case before the date of first ZA administration. Routine DXA scans performed within the outlined time window can be used as baseline DXA scans.

Subjects who do not fulfill the eligibility criteria for or do not consent to the ZA extension will complete OLP assessments only.

Subjects who participate in the ZA extension, will undergo the following assessments:

With:

Zoledronic Acid (ZA) Substudy:

A substudy has been added in Appendix G to evaluate subjects completing open-label denosumab treatment, to either receive a single dose of ZA, or to be managed according to current standard of care (SOC) for the patient population.

Subjects enrolled in the main study who received denosumab during the open label phase and are deemed eligible per the inclusion and exclusion criteria, may choose to participate in this substudy. Subjects that are not included in the substudy will end study as planned. Protocol-defined denosumab administration will complete at end of the open-label period no matter if subjects participate in the substudy or not.

Subjects enrolled in the substudy will be randomized to either receive a single dose of ZA (Therapy Arm) or will be managed according to the current SOC for this patient population (Control Arm). Day 1 for both arms is 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit. Follow up will continue for a total of 18 months after day 1.

Section: Protocol Synopsis (Exploratory Endpoints)

Remove:

~~Exploratory Endpoints:~~

[redacted]

Section: Protocol Synopsis (Exclusion Criteria)

Remove:

~~Subjects completing OL denosumab may be eligible for the ZA extension.~~

Section: Protocol Synopsis (Investigational Product Dosage and Administration in ZA Extension)

Remove:

~~Investigational Product Dosage and Administration in ZA Extension:~~

~~Therapy Arm: ZA 5 mg IV single dose~~

~~Control Arm: SOC~~

Section: Protocol Synopsis (Long-term Follow-up), Paragraph 6

Remove:

~~Post Open-label Denosumab Extension (ZA extension):~~

[redacted]

Section: Protocol Synopsis (Statistical Considerations)

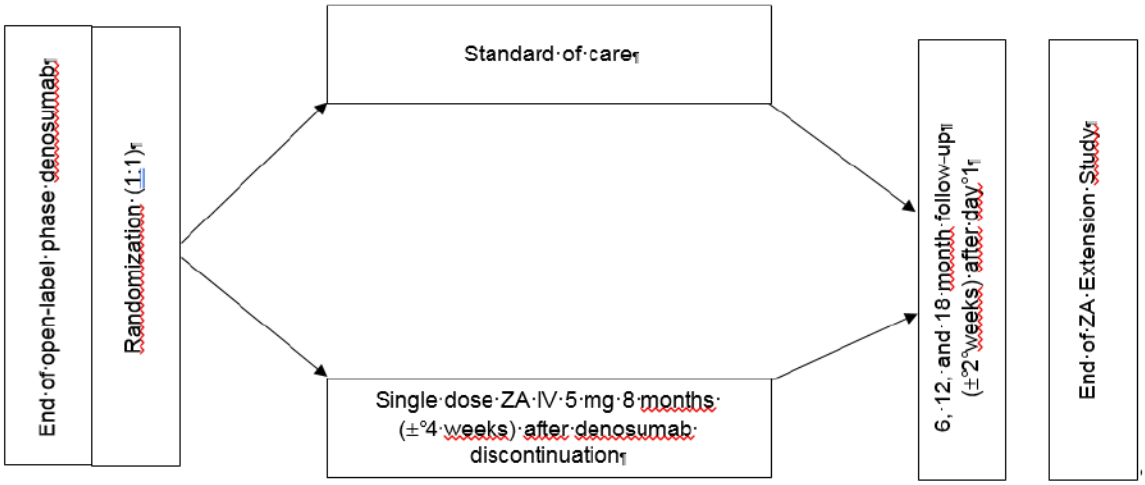
Remove:

~~Analysis of the endpoints from the ZA Extension will be descriptive only and will take place when all subjects randomized to the extension have attended their last study visit. The analyses will be performed after the final analysis of fracture related and disease-related outcomes for the main study.~~

Section: Study schema, Post Open-label Denosumab ZA Extension Study Design and Treatment Schema

Remove

~~Post Open-label Denosumab ZA Extension Study Design and Treatment Schema~~



~~IV = intravenous; ZA = zoledronic acid.~~

Section: Study Glossary

Final analysis	analysis performed after long-term follow up, **and OLP**, ~~approximately 66 months after PADCD, depending on the interim analysis~~

Section: 1.3 Exploratory, Bullet point 3

Remove:

[redacted]

Section: 2.3 Rationale

Remove:

~~BMD Changes After Open-label Denosumab Zoledronic Acid Extension (ZA Extension):~~

~~Denosumab cessation is associated with declines in bone mass that approach pre-treatment levels and available data do suggest an increase in multiple vertebral fractures after discontinuation. Bisphosphonate treatment after denosumab may be warranted to potentially prevent these fractures, particularly in patients not previously exposed to bisphosphonates and who remain at high fracture risk (ie, osteoporosis with previous vertebral fractures), but limited data are available confirming the validity of this hypothesis. Therefore, there is a data gap regarding optimal strategies for patients who will discontinue denosumab. The ABCSG18 Post Open-label Denosumab Extension (ZA Extension) is designed to evaluate on patients discontinuing denosumab, to either receive a single dose of ZA, or to be managed according to current standard of care (SOC) for respective patient population after denosumab discontinuation.~~

Section 3.1 Study Design

Replace:

Post Open-label Denosumab Zoledronic Acid Extension (ZA Extension):

[redacted]

After regulatory and IRB/IEC approval of Protocol Amendment 5, willing and eligible subjects who participated in the OLP of the study and completed OL denosumab may opt in this ZA extension and either receive a single dose of ZA (Therapy Arm), or are managed according to the current SOC for this patient population (Control Arm). Patients who completed OLP denosumab and ended study as defined per protocol are eligible to participate in the ZA extension trial as long as the outlined criteria are fulfilled.

Written consent may be obtained from date of the last OLP denosumab administration until 9 months after. The screening phase starts from date of the last OLP denosumab administration at the earliest and lasts until randomization, but must occur after written consent has been obtained.

Willing and eligible subjects who completed OL denosumab are randomized to 1 single 5 mg IV dose of ZA or to SOC. Randomization can be performed within 8 days prior to Day 1. Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit. Follow up will continue for a total of 18 months after day 1. Randomization will be stratified by AI use at the timepoint of OLP denosumab completion (Yes or No).

DXA scan can be performed between 7 to 9 months after the date of the last denosumab administration, but in any case before the date of first ZA administration. Routine DXA scans performed within the outlined time window can be used as baseline DXA scans.

Subjects who do not fulfill the eligibility criteria for or do not consent to the ZA extension will complete OLP assessments only.

Subjects who participate in the ZA extension, will undergo the following assessments:

[redacted]

In the event a serious or non-serious adverse event of special interest (oral event) or other SAE is identified outside the subjects' scheduled visits, the standard guidance in Section 9 should be followed.

With:

Zoledronic Acid (ZA) Substudy:

A substudy has been added in Appendix G to evaluate subjects completing open-label denosumab treatment, to either receive a single dose of ZA, or to be managed according to current standard of care (SOC) for the patient population.

Subjects enrolled in the main study who received denosumab during the open label phase and are deemed eligible per the inclusion and exclusion criteria, may choose to participate in this substudy. Subjects that are not included in the substudy will end study as planned. Protocol-defined denosumab administration will complete at end of the open-label period no matter if subjects participate in the substudy or not.

Subjects enrolled in the substudy will be randomized to either receive a single dose of ZA (Therapy Arm) or will be managed according to the current SOC for this patient population (Control Arm). Day 1 for both arms is 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit. Follow up will continue for a total of 18 months after day 1.

In the event **an** adverse event of special interest (**renal toxicity, clinically relevant hyper/hypocalcemia and** oral event) or other SAE is identified outside the subjects' scheduled visits, the standard guidance in Section 9 should be followed.

Section: 3.2 Number of Centers, Paragraph 2

Remove:

~~Approximately 30 sites in Austria are anticipated to participate in the ZA extension.~~

Section: 3.3 Number of Subjects, Paragraph 3

Remove:

~~Approximately 200 subjects are anticipated to participate in the ZA extension.~~

Section: 3.4 Estimated Study Duration

Remove:

The actual timing of analyses will be determined by the PADCD. Study duration is estimated to be 169 months, which includes an enrollment period of approximately 82 months, an end of the treatment phase (ie, the PADCD) of approximately 21 months and approximately 66 months following the PADCD for a 5 year long-term follow-up including an OLP (12 months unblinding option and a maximum of 36 months of treatment) (see Sections 7.15 and 10.5). ~~Amendment 5 (ZA extension) will add a maximum of approximately 27 months (considering that the patient may enter the extension study 9 months after OLP denosumab completion) to the study duration.~~

Section: 3.4.1 Study Duration for Participants, Paragraphs 2 and 3

Replace:

Subjects who receive open-label denosumab will be followed-up until completion of 36 months of treatment or approximately 66 months after PADCD, whichever is longer. Subjects in the OLP may consent to an extension to assess discontinuation from denosumab and receive either single dose ZA 5 mg IV or SOC treatment, which will be for a maximum duration of approximately 27 further months.
The expected time on study is up to approximately 196 months.

With:

Subjects who receive open-label denosumab will be followed-up until completion of 36 months of treatment or approximately 66 months after PADCD, whichever is longer. ~~Subjects in the OLP may consent to an extension to assess discontinuation from denosumab and receive either single dose ZA 5 mg IV or SOC treatment, which will be for a maximum duration of approximately 27 further months.~~
The expected time on study is up to approximately **169** months.

Section: 3.4 Estimated Study Duration

Remove:

~~3.4.5 Post Open-label Denosumab ZA Extension Treatment~~

~~Patients that completed their OLP denosumab visit and ended the study as defined per protocol are eligible to participate in the ZA extension as long as all inclusion/exclusion criteria are met.~~

~~Zoledronic acid will be administered 8 months (± 4 weeks) after last OLP administration for subjects randomized to treatment arm. Subjects randomized to SOC, will attend the site for visits at the same visit schedule as the treatment arm subjects.~~

~~Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit.~~

[redacted]

Section: 3.4.5 End of Study (Double-blind Phase and End of ZA substudy)

Replace:

3.4.5 End of Study **(**Double-blind Phase and OLP)

The end of the study will occur when the last subject has completed their last formal visit or last formal contact or an unscheduled study visit in case of early withdrawal from the study. This is expected to occur when the last subject completes the extension to the OL treatment period or their last scheduled LTFU visit.

With

3.4.5 End of Study (Double-blind Phase and **end of ZA Substudy)**

The end of the study will occur when the last subject has completed their last formal visit or last formal contact or an unscheduled study visit in case of early withdrawal from the study. This is expected to occur when the last subject completes the **ZA substudy**.

Section: 3.4. Estimated Study Duration

Remove:

~~3.4.7 End of Study of ZA Extension~~

~~The end of ZA Extension will occur when the last subject participating in the ZA Extension has completed their last formal visit or an unscheduled study visit in case of early withdrawal from the ZA extension.~~

~~End of study reasons include 3 early EOS reasons (death, lost to follow-up, and consent withdrawal) and per protocol EOS of ZA Extension.~~

Section: 4 SUBJECT ELIGIBILITY

Remove:

~~Section: 4.5 Inclusion Criteria for Post Open-label Denosumab Zoledronic Acid Extension (ZA Extension)~~

~~4.5 Inclusion Criteria for Post Open-label Denosumab Zoledronic Acid Extension (ZA Extension)~~

~~4.5.1 Obtain signed and dated written informed consent prior to performing any study-specific procedure~~

~~4.5.2 Subjects that received OLP denosumab and completed OLP treatment~~

~~4.5.3 Last OLP denosumab administration no longer than 9 months ago~~

~~Section: 4.6 Exclusion Criteria for Post Open-label Denosumab Zoledronic Acid Extension~~

~~Add:~~

~~4.6 Exclusion Criteria for Post Open-label Denosumab Zoledronic Acid Extension~~

~~4.6.1 Current or prior ZA administration.~~

~~4.6.2 Subjects who ended treatment with investigational product (IP) prematurely in the double-blind phase and OL phase~~

~~4.6.3 Known sensitivity or intolerance to any of the products to be administered during the study (eg, ZA, calcium or vitamin D)~~

~~4.6.4 Known history of any of the following conditions either by subject self report or chart review~~

- ~~Paget's disease (bone), Cushing's disease, hyperprolactinemia or other active metabolic bone disease~~
- ~~Known history of hypocalcemia~~
- ~~Major surgery, or significant traumatic injury occurring within 4 weeks prior to randomization~~
- ~~Parathyroid glands in neck surgically removed~~
- ~~Any sections of intestine removed~~
- ~~Known human immunodeficiency virus infection~~
- ~~Active infection with hepatitis B or hepatitis C virus~~

~~4.6.5 Known liver or renal disease as determined by the investigator and indicated by the following criteria:~~

- ~~Aspartate aminotransferase ≥ 2.5 x ULN~~
- ~~Alanine transaminase ≥ 2.5 x ULN~~
- ~~Serum creatinine ≥ 2 x ULN~~
- ~~Creatine clearance < 35ml/min~~

~~4.6.6 Subjects that are pregnant or breastfeeding~~

- ~~All subjects with reproductive potential must have a negative pregnancy test within 7 days before randomization~~

~~4.6.7 Subjects who are osteoporotic in baseline BMD~~

Section: 5 SUBJECT ENROLLMENT

Remove:

~~5.6 Post Open-label Denosumab ZA Extension~~

~~A subject will be assigned by an Interactive Voice/Web Response System to 1 of 2 treatment groups (ZA or SOC), in a 1:1 ratio. The randomization schedule will use randomly permuted blocks and will be stratified by AI use at the timepoint of OLP denosumab completion (Yes or No). A subject who is randomized to the ZA Extension will maintain the same subject number which is also the subject number as assigned in the double-blind study. A subject may only be randomized once into ZA Extension. The ZA randomization list will be generated and maintained by an Amgen representative not involved in the conduct of the study.~~

Section: 6.3 Prohibited Medication in Post Open-label Denosumab ZA Extension

Remove:

~~6.3 Prohibited Medication in Post Open-label Denosumab ZA Extension~~

~~Subjects participating in the ZA Extension will follow the same visit schedule as outlined in the ZA Extension (Appendix A, Schedule of Assessments). There are no prohibited medications in this extension.~~

~~6.3.1 Investigational Product (Denosumab)~~

~~No denosumab is required or provided for patients in the post OL denosumab extension.~~

~~6.3.2 Non Investigational Product Dosage, Administration, and Schedule~~

~~Subjects will be randomized 1:1 to receive a single 5 mg IV of ZA or SOC 8 months (± 4 weeks) after completing OLP.~~

~~For those subjects randomized to receive ZA, this will be administered slowly as a constant infusion rate. The infusion time must not be less than 15 minutes, after all other study visit procedures have been completed.~~

~~Zoledronic Acid must only be prescribed and administered to patients by healthcare professionals experienced in the administration of IV bisphosphonates. Patients treated with ZA should be given the package leaflet.~~

~~Any unused medicinal product or waste material should be disposed of in accordance with local requirements.~~

~~Refer to the summary of product characteristics (SmPC) (https://www.medicines.org.uk/emc/product/44/smpc) for detailed information on the administration of ZA.~~

~~6.3.3 Prohibited medications~~

~~There are no prohibited medications in the post OL denosumab extension.~~

Section: 7.7.1 Assessment of Clinical Fractures During Open-label Phase, Subtitle

Remove:

7.7.1 Assessment of Clinical Fractures During Open-label Phase ~~and ZA Extension~~

Section: 7 STUDY PROCEDURES

Remove:

[redacted]

~~7.13 Laboratory Assessments in ZA Study~~

~~Routine laboratory assessments to determine eligibility must be performed before randomization. Patients with child bearing potential must have a negative pregnancy test within 7 days prior to randomization. Subjects who have undergone a hysterectomy do not require a pregnancy test.~~

[redacted]

Table 1. Serum and Blood Sample Analyte Listing

Serum Chemistry	Hematology	Other
Sodium	Red blood cells	**Denosumab antibody assay (only double-blind study)**
Potassium	Hemoglobin	[redacted]
Calcium	Hematocrit	
Blood Urea Nitrogen/Urea	Platelets	
Creatinine	White blood cells	
Total bilirubin		
Alkaline phosphatase		
Alanine transaminase		
Asparate aminotransferase		
LDH		
Gamma GT		
Albumin		

[redacted]

[redacted]

Section: 7.15 Adverse Events, Open-label Phase/Long-term Follow-up

Remove:

~~Post Open-label Denosumab Zoledronic Acid Extension (ZA Extension):~~

~~During the post OL denosumab extension, (S)AEs of special interest (causal relationship to ZA and oral events) will be documented for subjects receiving ZA.~~

~~New clinical fractures will be collected and any suspected atypical femoral fracture (femur midshaft fracture, femur subtrochanteric, or femur distal) associated with minimal trauma will be classified as an SAE for all subjects (see Section 9.1.2), and should be recorded on a Serious Adverse Event Report form (see Appendix F) and faxed to the local Amgen Safety Specialist within 24 hours of discovery or notification of the event (see Section 9.3).~~

Section: 7 STUDY PROCEDURES

Remove:

~~7.20 Post OL Denosumab Zoledronic Acid Extension (ZA Extension)~~

~~Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit.~~

~~Follow up will continue for a total of 18 months after day 1.~~

[redacted]

Section: 7.18 End of Study, Paragraph 1

Remove:

The patient individual EOS is defined as the last formal visit or contact for a subject or an unscheduled study visit in case of early withdrawal from study. ~~The overall EOS will occur when the last subject has completed their last formal visit or last formal contact or an unscheduled study visit in case of early withdrawal from the study. This is expected to occur when the last subject completes their end of open label treatment visit or their last scheduled LTFU visit.~~

Section: 7 STUDY PROCEDURES

Remove:

~~7.22 End of Study of ZA Extension~~

~~The end of ZA extension will occur when the last subject participating in the ZA extension has completed their last formal visit or an unscheduled study visit in case of early withdrawal from the ZA extension.~~

~~End of ZA extension study will be 18 months after day 1.~~

~~End of study reasons include 3 early EOS reasons (death, lost to follow up, consent withdrawal) and per protocol EOS of ZA extension.~~

Section: 9.3.1 Adverse Events of Special Interest and Serious Adverse Event Reporting During the Open-label Phase

Remove:

9.3.1 Adverse Events of Special Interest and Serious Adverse Event Reporting During the Open-label Phase ~~and Post Open label Denosumab Extension~~

Section: 9.3.1.2, Serious Adverse Event Reporting, Paragraphs 3 and 4

Remove:

~~For subjects participating in the post OL denosumab extension and receiving ZA, the investigator is responsible for ensuring all SAEs observed by the investigator or reported by the subject that occur after signing the ICF for the extension until the last study visit (18 months after Day 1), are recorded in the subjects medical record and are submitted to Amgen. New clinical fractures will be collected and any suspected atypical femoral fracture (femur midshaft fracture, femur subtrochanteric, or femur distal) associated with minimal trauma will be classified as an SAE for all subjects (see Section 9.1.2), and should be recorded on a Serious Adverse Event Report form (see Appendix F) and faxed to the local Amgen Safety Specialist within 24 hours of discovery or notification of the event (see Section 9.3).~~

~~In addition, any suspected atypical femoral fracture (femur midshaft fracture, femur subtrochanteric, or femur distal) associated with minimal trauma will be classified as an SAE for all subjects, and should be recorded in the subject's medical record and submitted to Amgen (see Appendix F Clinical Trial Serious Adverse Event report form)~~

~~and recorded in the applicable fracture recording CRF. SAE reporting period for suspected atypical femoral fracture will be until EOS.~~

Section: 10.1 Study Design, Paragraph 2

Remove:

[redacted]

Section: 10.2.4 Exploratory Endpoints

Remove:

[redacted]

Section: 10.2.5 Subsets, Paragraphs 2 and 3

Remove:

[redacted]

[redacted]

Section: 10.3 Sample Size Considerations, Paragraphs 6 to 10

Remove:

~~For the ZA extension, it is expected that approximately 200 subjects could be randomized.~~

~~Data is limited on BMD for subjects who discontinue denosumab 60 mg Q6M in the oncology setting. Therefore data from postmenopausal osteoporosis was used in the sample size.~~

~~A phase 2 randomized blinded clinical trial in postmenopausal women with low bone mass assessed the effect of denosumab 60 mg Q6M on BMD and bone turnover markers (CTX and Osteocalcin) after long-term continued, discontinued, and restarting of therapy (Miller et al, 2008). One of the treatment cohorts received denosumab 210 mg Q6M for 24 months then placebo for the next 24 months. Based on this study, a 5% (SD = 4.3%), 5.2% (SD = 2.6%), and 3.9% (SD = 3.8%) decrease in the lumbar spine, total hip, and femoral neck BMD was seen during the 2 years after denosumab discontinuation (data on file).~~

~~A paper reporting 22 case studies of postmenopausal women who received 5 injections (approximately 2.5 years) of denosumab 60 mg Q6M and were then given a single dose of ZA 6 months after the fifth injection (Lehmann and Aeberli, 2017). A 3.8% (SD = 2.8%), 1.7% (SD = 3.3%), and 0.6% (SD = 5%) decrease in the lumbar spine, total hip, and femoral neck BMD was seen during the 2.5 years after denosumab discontinuation.~~

~~A table showing the level of precision (ie, half width of 95% CI) for each treatment arm and each BMD type for different sample sizes, calculated based on the standard deviations estimated from the 2 studies mentioned above, is presented below.~~

~~Table 2. Sample Sizes~~

~~Number of subjects in each arm~~	~~Precision (half width of 95% confidence interval)~~					
	~~Standard of care~~			~~IV zoledronic acid~~		
	~~Lumbar Spine~~	~~Total Hip~~	~~Femoral Neck~~	~~Lumbar Spine~~	~~Total Hip~~	~~Femoral Neck~~
~~75~~	~~± 1.0%~~	~~± 0.6%~~	~~± 0.9%~~	~~± 0.6%~~	~~± 0.8%~~	~~± 1.1%~~
~~100~~	~~± 0.9%~~	~~± 0.5%~~	~~± 0.7%~~	~~± 0.5%~~	~~± 0.7%~~	~~± 1.0%~~
~~125~~	~~± 0.8%~~	~~± 0.5%~~	~~± 0.7%~~	~~± 0.5%~~	~~± 0.6%~~	~~± 0.9%~~

~~IV = intravenous~~

Section: 10.4 Access to Individual Subject Treatment Assignments, Paragraph 5

Remove:

~~Eligible subjects who consent to the ZA extension do not receive any investigational product (denosumab), but will be randomized 1:1 to receive single dose ZA 5 mg IV or SOC.~~

Section: 10.5 Interim Analysis, Early Stopping Guidelines, and Time-points of Analyses

Remove:

[redacted]

Section: 10.6.2.4 Exploratory Analyses

Remove:

[redacted]

[redacted]

Section: 11.1 Denosumab

Remove:

~~Post Open-label Denosumab ZA Extension:~~

~~No ZA will be provided for this extension.~~

~~Patients included in the treatment arm of the ZA extension will obtain ZA (IV 5 mg) via a prescription from their physician.~~

~~There are currently no guidelines or evidence regarding the best strategy to be considered when discontinuing denosumab in cancer treatment-induced bone loss. There has been expert opinion published stating that a transition to a bisphosphonate represents a treatment option (Hadji et al, 2017).~~

Section: 11.2 Access to Treatment Assignments

Remove:

~~11.2.3 Post Open-label Denosumab ZA Extension~~

~~After the ICF is signed, randomization of subjects deemed eligible for the ZA Extension can occur, and ZA shall be administered 8 months (± 4 weeks) from the last dose of OL denosumab.~~

~~Patients included in the ZA arm of the post denosumab discontinuation OL administration will obtain ZA (IV 5 mg) via a prescription from their physician.~~

~~Refer to the SmPC (https://www.medicines.org.uk/emc/product/44/smpc) for detailed information on the administration of ZA.~~

Section: 14 References

Remove:

~~Hadji P, Aapro MS, Body JJ, Gnant M, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. *J Bone Oncol*. 2017; 23;7:1-12.~~

~~Lehmann T, Aeberli D. Possible protective effect of switching from denosumab to zoledronic acid on vertebral fractures. *Osteoporos Int*. 2017;28(10):3067-3068.~~

~~Miller PD, Bolognese MS, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinding phase 2 clinical trial. *Bone*. 2008;43(2):222-229.~~

Section: 15 Appendix A

Remove:

~~Schedule of Assessments for Post Open-label Denosumab Zoledronic Acid Extension (ZA Extension)~~

~~Study assessment~~	~~Screening/baseline~~	~~Randomization~~	~~Q6M Visit~~	~~Q12M Visit~~	~~Q18M Visit = EOS[a]~~
~~Re-consent~~	~~X~~				
~~Randomization~~		~~X~~			
~~IV Zoledronic acid (5mg x 1)[b]~~		~~X~~			
[redacted]					
~~Laboratory Assessment[c]~~	~~X~~				

[redacted]

[redacted] ~~EOS= end of study; IV = intravenous; M = month;OL = open-label; OLP = open-label phase; QXM= every X months;~~ [redacted] ~~SOC = standard of care; ZA = zoledronic acid..~~

~~The screening phase starts from date of the last OLP denosumab administration at the earliest and lasts until randomization but must occur after written consent has been obtained.~~

~~Written consent may be obtained from date of the last OLP denosumab administration until 9 months after.~~

~~Randomization can be performed within 8 days prior to Day 1.~~

~~Visits to site: Day 1 after re-consent and randomization, 6, 12, and 18 months (± 2 weeks) after day 1.~~

~~[a] EOS: End of ZA extension study will be 18 months after day 1; or the last scheduled visit in case patient ends study prematurely.~~

~~[b] ZA administration must take place within 8 days after randomization. Half of the patients will be randomized to SOC (No ZA). Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit. Visits will take place 6, 12, 18 months after day 1.~~

[redacted]

[redacted]

[a] ~~Routine laboratory assessments to determine eligibility must be performed before randomization. A negative pregnancy test within 7 days prior to randomization.~~

[redacted]

Section: Appendix G Zoledronic Acid Substudy

Appendix F. Serious Adverse Event Form

1. EXPLORATORY OBJECTIVE

[redacted]

2. RATIONALE

Denosumab cessation is associated with declines in bone mass that approach pre-treatment levels and available data do suggest an increase in multiple vertebral fractures after discontinuation. Bisphosphonate treatment after denosumab may be warranted to potentially prevent these fractures, particularly in patients not previously exposed to bisphosphonates and who remain at high fracture risk (ie, osteoporosis with previous vertebral fractures), but limited data are available confirming the validity of this hypothesis. Therefore, there is a data gap regarding optimal strategies for patients who will discontinue denosumab. The ZA substudy is designed to evaluate subjects completing open-label denosumab treatment, to either receive a single dose of ZA, or to be managed according to current standard of care (SOC) for respective patient population. Standard of Care (SoC) for this substudy patient population depends on individual factors such as bone density, lifestyle recommendations by the Investigator such as diet, physical activities and sun exposure, as well as local treatment standards and will be agreed upon with the treating Investigator.

There are currently no guidelines or evidence regarding the best strategy to be considered when discontinuing denosumab in cancer treatment-induced bone loss. There has been expert opinion published stating that a transition to a bisphosphonate represents a treatment option (Hadji et al, 2017).

3. EXPERIMENTAL PLAN

3.1. Substudy Design

[redacted]

After regulatory and IRB/IEC approval of Protocol Amendment 6 (added ZA substudy), willing and eligible subjects who participated in the OLP of the study and completed OL denosumab may opt in this ZA substudy and either receive a single dose of ZA (Therapy Arm), or are managed according to the current SOC for this patient population (Control Arm). Subjects who completed OLP denosumab are eligible to participate in the ZA substudy as long as the outlined criteria are fulfilled.

Written consent may be obtained from date of the last OLP denosumab administration until 9 months after. The screening phase starts from date of the last OLP denosumab administration at the earliest and lasts until randomization, but must occur after written consent has been obtained.

Willing and eligible subjects who completed OL denosumab are randomized to 1 single 5 mg IV dose of ZA or to SOC. Randomization can be performed within 8 days prior to Day 1. Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit. Follow up will continue for a total of 18 months after day 1. Randomization will be stratified by AI use at the timepoint of OLP denosumab completion (Yes or No).

After day 1, subjects will be evaluated every 6 months. DXA scan can be performed between 7 to 9 months after the date of the last denosumab administration, but in any case before the date of first ZA administration. Routine DXA scans performed within the outlined time window can be used as baseline DXA scans.

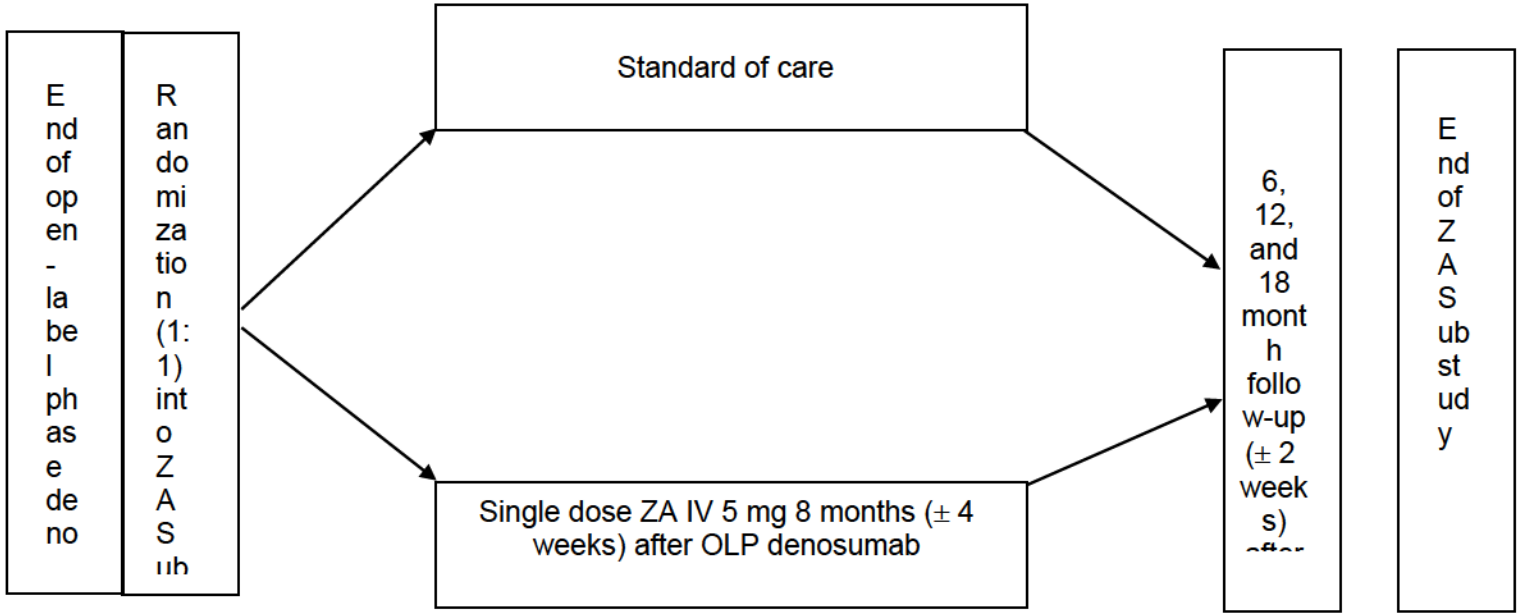
Subjects who do not fulfill the eligibility criteria for or do not consent to the ZA substudy will complete OLP assessments only.

Subjects who participate in the ZA substudy, will undergo the following assessments:

[redacted]

3.2. Schema

ZA Substudy Design and Treatment Schema



IV = intravenous; ZA = zoledronic acid.

3.3. Number of Centers

Approximately 30 sites in Austria are anticipated to participate in the ZA substudy.

3.4. Number of Subjects

Approximately 200 subjects are anticipated to participate in the ZA substudy.

3.5. Estimated Substudy Duration

3.5.1. Estimated Substudy Duration for Participants

Subjects will be in this substudy for a maximum duration of approximately 27 months.

3.5.2. ZA Substudy Treatment

Subjects that completed their OLP denosumab visit are eligible to participate in the ZA substudy as long as all the substudy inclusion/exclusion criteria are met.

Zoledronic acid will be administered 8 months (± 4 weeks) after last OLP administration for subjects randomized to treatment arm. Subjects randomized to SOC, will attend the site for visits at the same visit schedule as the treatment arm subjects.

Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit.

[redacted]

3.5.3. End of ZA Substudy

The end of ZA substudy will occur when the last subject participating in the ZA substudy has completed their last formal visit or an unscheduled study visit in case of early withdrawal from the ZA substudy.

End of study reasons include 3 early EOS reasons (death, lost to follow-up, and consent withdrawal) and per protocol EOS of ZA substudy.

4. ELIGIBILITY CRITERIA

4.5. Inclusion Criteria for ZA Substudy

4.5.1. Obtain signed and dated written informed consent prior to performing any substudy-specific procedure

4.5.2. Subjects that received OLP denosumab and completed OLP treatment

4.5.3. Last OLP denosumab administration no longer than 9 months ago

4.6. Exclusion Criteria for ZA Substudy

4.6.1. Current or prior ZA administration.

4.6.2. Subjects who ended treatment with investigational product (IP) prematurely in the double-blind phase and OL phase

4.6.3. Known sensitivity or intolerance to any of the products to be administered during the substudy (eg, ZA, calcium or vitamin D)

4.6.4. Known history of any of the following conditions either by subject self report or chart review

- Paget's disease (bone), Cushing's disease, hyperprolactinemia or other active metabolic bone disease
- Known history of hypocalcemia
- Major surgery, or significant traumatic injury occurring within 4 weeks prior to randomization
- Parathyroid glands in neck surgically removed.
- Any sections of intestine removed.
- Known human immunodeficiency virus infection
- Active infection with hepatitis B or hepatitis C virus

4.6.5. Known liver or renal disease as determined by the investigator and indicated by the following criteria:

- Aspartate aminotransferase ≥ 2.5 x ULN
- Alanine transaminase ≥ 2.5 x ULN
- Serum creatinine ≥ 2 x ULN
- Creatine clearance < 35ml/min

4.6.6. Subjects that are pregnant or breastfeeding

- All subjects with reproductive potential must have a negative pregnancy test within 7 days before randomization

4.6.7. Subjects who are osteoporotic in baseline BMD

5. SUBJECT ENROLLMENT

A subject will be assigned by an Interactive Voice/Web Response System to 1 of 2 treatment groups (ZA or SOC), in a 1:1 ratio. The randomization schedule will use randomly permuted blocks and will be stratified by AI use at the timepoint of OLP denosumab completion (Yes or No). A subject who is randomized to the ZA substudy will maintain the same subject number which is also the subject number as assigned in the double-blind (main) study. A subject may only be randomized once into ZA substudy. The ZA randomization list will be generated and maintained by an Amgen representative not involved in the conduct of the study.

6. TREATMENT PROCEDURES

6.1. Investigational Product (Zoledronic Acid) Dosage, Administration, and Schedule

Subjects will be randomized 1:1 to receive a single 5 mg IV of ZA or SOC 8 months (± 4 weeks) after completing OLP.

For those subjects randomized to receive ZA, this will be administered slowly as a constant infusion rate. The infusion time must not be less than 15 minutes, after all other study visit procedures have been completed.

Zoledronic Acid must only be prescribed and administered to subjects by healthcare professionals experienced in the administration of IV bisphosphonates. Subjects treated with ZA should be given the package leaflet. ZA will be locally provided by participating sites and will be reimbursed by the sponsor.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.Refer to the summary of product characteristics (SmPC) (https://www.ema.europa.eu/en/medicines/human/EPAR/zometa#product-information-section) for detailed information on the administration of ZA.

6.2. Prohibited medications

There are no prohibited medications in the ZA substudy.

7. STUDY PROCEDURES

[redacted]

7.4. Laboratory Assessments

As described in eligibility criteria for this substudy, routine laboratory assessments (at least for ALT, AST, serum creatinine, creatine clearance and calcium) to determine eligibility must be performed before randomization. Patients with child bearing potential must have a negative pregnancy test within 7 days prior to randomization. Subjects who have undergone a hysterectomy do not require a pregnancy test.

[redacted]

Additionally, subjects will have lab assessments to determine eligibility as outlined in Table 2.

Table 2. Serum and Blood Sample Analyte Listing for ZA Substudy

Serum Chemistry	Hematology	Other
Sodium	Red blood cells	[redacted]
Potassium	Hemoglobin	
Calcium[a]	Hematocrit	
Blood Urea Nitrogen/Urea	Platelets	
Creatinine[a]	White blood cells	
Total bilirubin		
Alkaline phosphatase		
Alanine transaminase[a]		
Asparate aminotransferase[a]		
LDH		
Gamma GT		
Albumin		

[redacted]

8. ADVERSE EVENT REPORTING

During the substudy, all SAEs and AEs of special interest (renal toxicity, clinically relevant hyper/hypocalcemia, and oral events) will be documented from signing the ICF for the ZA substudy until the last study visit (18 months after Day 1) in the Adverse Event eCRF.

For subjects participating in the substudy, the investigator is responsible for ensuring all SAEs observed by the investigator or reported by the subject that occur after signing of the ICF for the ZA substudy until the last study visit (18 months after Day 1), are recorded in the subjects medical record, the Adverse Event eCRF, and are submitted to Amgen.

New clinical fractures will be collected and any suspected atypical femoral fracture (femur midshaft fracture, femur subtrochanteric, or femur distal) associated with minimal trauma will be classified as an SAE for all subjects (see Section 9.1.2), and should be recorded in the subject's medical record, applicable fracture-recording CRF, and on a Serious Adverse Event Report form (see Appendix F) then faxed to the local Amgen Safety Specialist within 24 hours of discovery or notification of the event (see Section 9.3).

SAE reporting period for suspected atypical femoral fracture will be until EOS.

9. STATISTICAL CONSIDERATIONS

9.1. Exploratory Endpoints

[redacted]

9.2. Subsets

[redacted]

9.3. Sample Size Considerations

For the ZA substudy, it is anticipated that approximately 200 subjects could be randomized.

Data is limited on BMD for subjects who discontinue denosumab 60 mg Q6M in the oncology setting. Therefore, data from postmenopausal osteoporosis was used in the sample size.

A phase 2 randomized blinded clinical trial in postmenopausal women with low bone mass assessed the effect of denosumab 60 mg Q6M on BMD and bone turnover markers (CTX and Osteocalcin) after long-term continued, discontinued, and restarting of therapy (Miller et al, 2008). One of the treatment cohorts received denosumab 210 mg Q6M for 24 months then placebo for the next 24 months. Based on this study, a 5% (SD = 4.3%), 5.2% (SD = 2.6%), and 3.9% (SD = 3.8%) decrease in the lumbar spine, total hip, and femoral neck BMD was seen during the 2 years after denosumab discontinuation (data on file).

A paper reporting 22 case studies of postmenopausal women who received 5 injections (approximately 2.5 years) of denosumab 60 mg Q6M and were then given a single dose of ZA 6 months after the fifth injection (Lehmann and Aeberli, 2017). A 3.8% (SD = 2.8%), 1.7% (SD = 3.3%), and 0.6% (SD = 5%) decrease in the lumbar spine, total hip, and femoral neck BMD was seen during the 2.5 years after denosumab discontinuation.

A table showing the level of precision (ie, half width of 95% CI) for each treatment arm and each BMD type for different sample sizes, calculated based on the standard deviations estimated from the 2 studies mentioned above, is presented below.

Table 3. Sample Sizes

Number of subjects in each arm	Precision (half width of 95% confidence interval)					
	Standard of care			IV zoledronic acid		
	Lumbar Spine	Total Hip	Femoral Neck	Lumbar Spine	Total Hip	Femoral Neck
75	± 1.0%	± 0.6%	± 0.9%	± 0.6%	± 0.8%	± 1.1%
100	± 0.9%	± 0.5%	± 0.7%	± 0.5%	± 0.7%	± 1.0%
125	± 0.8%	± 0.5%	± 0.7%	± 0.5%	± 0.6%	± 0.9%

IV = intravenous

9.4. Access to Individual Subject Treatment Assignments

Subjects in ZA substudy will be randomized 1:1 to receive single dose ZA 5 mg IV (investigational product) or SOC.

9.5. Timepoint of Analysis

[redacted]

9.6. Planned Methods of Analysis

[redacted]

[redacted] Analyses will be conducted on the ZA analysis set.

[redacted]

[redacted] will be summarized by treatment group on the ZA safety analysis set.

10. REFERENCES

Hadji P, Aapro MS, Body JJ, Gnant M, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. *J Bone Oncol.* 2017; 23;7:1-12.

Lehmann T, Aeberli D. Possible protective effect of switching from denosumab to zoledronic acid on vertebral fractures. *Osteoporos Int.* 2017;28(10):3067-3068.

Miller PD, Bolognese MS, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinding phase 2 clinical trial. *Bone.* 2008;43(2):222-229.

11. SCHEDULE OF ASSESSMENTS

Table 4. Schedule of Assessments for ZA Substudy

Study assessment	Screening/baseline	Randomization	Q6M Visit	Q12M Visit	Q18M Visit = EOS[a]
Re-consent	X				
Randomization		X			
IV Zoledronic acid (5mg x 1)[b]		X			
[redacted]					
Laboratory Assessment[e]	X				
[redacted]					

[redacted] EOS= end of study; IV = intravenous; M = month; OL = open-label; OLP = open-label phase; QXM= every X months; [redacted] SOC = standard of care; ZA = zoledronic acid.

The screening phase starts from date of the last OLP denosumab administration at the earliest and lasts until randomization but must occur afterwritten consent has been obtained.

Written consent may be obtained from date of the last OLP denosumab administration until 9 months after.

Randomization can be performed within 8 days prior to Day 1.

Visits to site: Day 1 after re-consent and randomization, 6, 12, and 18 months (± 2 weeks) after day 1.

[a] EOS: End of ZA substudy will be 18 months after day 1; or the last scheduled visit in case patient ends study prematurely.

[b] ZA administration must take place within 8 days after randomization. Half of the patients will be randomized to SOC (No ZA). Day 1 for both arms should be 8 months (± 4 weeks) from the last dose of OL denosumab. For the ZA arm, ZA will be administered on this visit. Visits will take place 6, 12,

[redacted]

[e] Routine laboratory at least for ALT, AST, serum creatinine, creatine clearance and calcium assessments to determine eligibility must be performed before randomization. A negative pregnancy test within 7 days prior to randomization has to be available for women of childbearing potential. Subjects who have undergone a hysterectomy do not require a pregnancy test

[redacted]

12. PHARMACY GUIDE FOR ZA SUBSTUDY

ZA Substudy Investigational Product (Zoledronic Acid) Dosage, Administration, and Schedule

Subjects will be randomized 1:1 to receive a single 5 mg IV of ZA or SOC 8 months (± 4 weeks) after completing OLP.

For those subjects randomized to receive ZA, this will be administered slowly as a constant infusion rate. The infusion time must not be less than 15 minutes, after all other study visit procedures have been completed.

Zoledronic Acid must only be prescribed and administered to subjects by healthcare professionals experienced in the administration of IV bisphosphonates. Subjects treated with ZA should be given the package leaflet. ZA will be locally provided by participating sites and will be reimbursed by the sponsor.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Amendment 5

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study to Determine the Treatment Effect of Denosumab in Subjects With Non-Metastatic Breast Cancer Receiving Aromatase Inhibitor Therapy

Amgen Protocol Number 20050209

ABCSG Protocol Number ABCSG 18

EudraCT Number 2005-005275-15

NCT00556374

Amendment Date: 01 April 2019

Rationale:

This protocol is being amended to:

- Add a randomization on patients still on open label denosumab to be treated with either a bisphosphonate or standard of care upon denosumab discontinuation
- Add exploratory objective to [redacted]
- Update the timing of ZA dose to 8 months (± 4 weeks) from the last dose of open-label denosumab because this is the moment where there is increase in the bone turnover marker, CTX, making it then the optimal moment for ZA to act
- Clarify that C-terminal telopeptide data will be collected during post open-label denosumab extension at specified times
- Clarify time periods for assessment during the extension to the open-label phase.
- Clarify analysis of the endpoints following the post open-label denosumab extension
- Add schema describing post open-label denosumab discontinuation extension
- Specify the approximate number of study sites in Austria participating in the post open-label denosumab extension
- Specify the approximate number of subjects participating in the post open-label denosumab extension

- Add a maximum of approximately 18 months to the study duration
- Add inclusion and exclusion criteria for post open-label denosumab zoledronic acid extension
- Add exclusion criteria for double-blind phase of the study
- Extend the expected time on study
- Clarify the End of Study definition
- Clarify that during the post open-label denosumab extension, no investigational product will be provided
- Make editorial and administrative changes for grammatical reasons as well as for internal consistency within the protocol.

Superseding Amendment 4

Protocol Title: A Randomized, Double-blind, Placebo-controlled, Multi-center Phase 3 Study to Determine the Treatment Effect of Denosumab in Subjects With Non-metastatic Breast Cancer Receiving Aromatase Inhibitor Therapy

Amgen Protocol Number 20050209/ABCSG-18

Superseding Amendment Date: 22 February 2016

Rationale:

Superseding Amendment 4 was written to:

- correct inconstant wording as it occurs in the document
- correct typographical and formatting errors
- clarify exploratory analysis wording in the statistical analysis section
- clarify/expand final analysis wording in the synopsis

Amendment 4

Protocol Title: A Randomized, Double-blind, Placebo-controlled, Multi-center Phase 3 Study to Determine the Treatment Effect of Denosumab in Subjects With Non-metastatic Breast Cancer Receiving Aromatase Inhibitor Therapy

Amgen Protocol Number Denosumab 20050209

ABCSG Protocol Number ABCSG 18

Amendment Date:	13 March 2006 FINAL 27 April 2006 Superseding Version 12 June 2006 Amendment 1 06 April 2010 Amendment 2 15 August 2012 Amendment 3 02 November 2012 Superseding Amendment 3 27 November 2012 Superseding 2 Amendment 3 25 January 2013 Superseding 3 Amendment 3 **25 January 2016 Amendment 4**

Rationale:

- **The key protocol change is the addition of an open-label phase during which denosumab will be offered to subjects who received placebo previously during the study and the extension of the long-term follow-up to 66 months after PADCD**.

The primary analysis at primary analysis data cut-off date (PADCD) demonstrated a treatment benefit with denosumab treatment and consequently the Data Monitoring Committee (DMC) recommended that:

- The study should continue out to 66 months after PADCD as disease-free survival (DFS) interim results did not indicate futility.
- Analysis for efficacy of the secondary endpoints should be conducted at or around 18 months after PADCD before unblinding to protect the integrity of the secondary endpoints.
- Denosumab should be offered to subjects who had previously received placebo but not before 18 months post PADCD.

Consequently, subjects who received placebo on study will be offered denosumab 60 mg every 6 months in addition to standard of care for 3 years (7 doses).

Previously, at yearly visits after PADCD, subjects would have been in long-term follow-up with standard of care for a period of either 18 or 66 months after PADCD (choice dependent on DMC recommendation) and analysis of DFS, bone

metastases-free survival (BMFS), and overall survival (OS) would have occurred at the end of the long-term follow-up.

- **Rationale section**

A presentation of the Austrian Breast and Colorectal Cancer Study Group (ABCSG) 18 primary analysis results was added to the rationale section to put the DMC recommendations in context.

- **Study procedural changes**

Study procedural changes applicable to two different subject groups (those who receive open-label treatment and those who do not) are required to align with the addition of an open-label phase.

Placebo-treated subjects who do not choose to receive open-label denosumab will be followed once a year (Q12M) by clinic visits or telephone contacts for:

- DFS, BMFS, and OS
- Clinical fracture recording (including serious adverse event [SAE] reporting of suspected atypical femoral fracture cases)
- Concomitant bone affecting medication
    - Bone targeted therapy (eg, bisphosphonate or denosumab)
    - Glucocorticoids
    - Antiepileptic drugs
    - Antidepressants
    - Insulin
- Anti-cancer related therapy (eg, chemotherapy or endocrine therapy)
- Supplements (vitamin D and calcium)

Subjects who receive open-label denosumab will attend clinic visits every 6 months for (Q6M):

- Administration of denosumab (60 mg subcutaneously [SC])
- Collection of serious and nonserious adverse events [(S)AEs] of special interest (oral events) and SAEs
- Clinical fracture recording (including SAE reporting of suspected atypical femoral fracture cases) (Q12M only)
- DFS, BMFS, and OS (Q12M only)
- Concomitant bone affecting medication (Q12M only)
    - Bone targeted therapy (eg bisphosphonate or denosumab)
    - Glucocorticoids
    - Antiepileptic drugs

  - Antidepressants
  - Insulin
- Anti-cancer related therapy (eg, chemotherapy or endocrine therapy) (Q12M only)
- Supplements (vitamin D and calcium) (Q12M only)

In addition, for all subjects, bone mineral density (BMD) data will be collected at any time a dual X-ray absorptiometry (DXA) scan is performed for BMD analysis as standard of care from PADCD to end of study.

The end of open-label treatment is defined for each subject as the point in time the last dose of denosumab is administered.

- **Exploratory objective**

New exploratory research was planned:

[redacted]

- **Inclusion/Exclusion Criteria to Receive Open-label Phase Denosumab**

Three inclusion criteria and five exclusion criteria were added to main study inclusion/exclusion to define the population eligible to receive treatment in the open-label phase.

- **Long-term follow-up**

Long-term follow-up will be approximately 66 months after PADCD for all subjects (or completion of treatment, whichever is longer), for subjects who receive open-label denosumab, as per the DMC recommendation, and to ensure that all subjects are able to receive the recommended seven doses of denosumab.

- **Unblinding**

Unblinding is necessary to identify subjects who received placebo during the double-blind phase. To maintain subject confidentiality, unblinding of subjects will be done by authorized site personnel using the unblinding (code break) call with the IVRS call center. The first dose of denosumab must be administered within 8 days of unblinding.

- **Concomitant medications**

A section describing use and documentation of concomitant medications was added to the protocol for the open-label phase to ensure that all concomitant medications recognized and documented to have an impact on bone modelling were captured.

- **Prohibited therapy**

A section describing prohibited therapy (ie, bisphosphonates) was added to the protocol for the open-label phase. Bisphosphonates language was maintained in the open-label phase to protect the study endpoint.

- **Dosing**

Sections describing dosing, including denosumab dose, dosing frequency and duration, overdose, missed doses, and dose adjustments were added to the protocol for the open-label phase.

- **Clinical fractures**

[redacted]

- **DXA and bone mineral density data**

A section describing documentation of BMD data from DXA performed as standard of care during the open-label phase was added to the protocol.

- **Adverse events**

A section describing documentation of [redacted] was added to the protocol for the open-label phase to allow for [redacted]. Handling of clinical fractures during open-label treatment and any suspected atypical femoral fracture, classified as an SAE, was also described.

- **Early withdrawal**

A description of the follow-up required for subjects who withdraw from denosumab during the open-label phase was added to the protocol for operational reasons. For completeness, survival data will be collected every 12 months for up to approximately 66 months after PADCD.

- **End of open-label treatment**

As during the double-blind phase, subjects will complete an end of open-label treatment visit 30 to 45 days after the last dose of open-label denosumab.

- **Long-term follow-up**

A description of long-term follow-up for subjects who do and do not receive open-label denosumab was added since there are differences for each group of subjects.

- **Adverse events of special interest and SAE reporting**

For operational reasons, sections describing reporting of all SAEs and adverse events of special interest were added to the protocol for the open-label phase.

- **Statistical analysis**

The statistical analysis section of the protocol was altered to add a time-driven analysis for efficacy of the secondary endpoint DFS, which will take place approximately 18 months after PADCD, before unblinding of subjects at the investigator/subject level has occurred.

Primary, secondary and safety endpoints will be analyzed in a final analysis at the end of the study. The DFS analysis at approximately 18 months after PADCD will be considered the main DFS analysis for the hierarchical testing strategy, with the [redacted] considered exploratory.

The subject incidence rates of [redacted] reported during the open-label phase will be tabulated separately by system organ class and preferred term.

- **Investigational product**

A description of the denosumab product that will be supplied for use during the open-label phase was added.

- **Administrative**

Minor text clarifications, additions and corrections, as well as typographical, format, and administrative changes were made throughout the protocol. The key sponsor contact information was updated to align with current personnel.

Amendment 3

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study to Determine the Treatment Effect of Denosumab in Subjects with Non-Metastatic Breast Cancer Receiving Aromatase Inhibitor Therapy

Denosumab

Amgen Protocol Number: 20050209

ABCSG Protocol number: ABCSG-18

Amendment Date: 25 January 2013

Rationale:

The primary reason for this amendment is to clarify the definition of post-menopausal status for subjects < 60 years of age. This change will clarify that for subjects < 60 years of age, FSH and estradiol must be in the post-menopausal range and if the subject has had a previous hysterectomy, there is no requirement for a pregnancy test.

The definition of termination date has been updated to a primary analysis data cut-off date (PADCD) and a 1 or 5 year follow-up has been added.

The investigational product currently being used on this study will expire and the investigational product will be switched from vials to a pre-filled syringe.

Other Changes

In addition the following additional changes are being proposed:

- Clarify eligibility criteria for post-menopausal status
- To clarify the procedures regarding the End of Treatment visit.
- Clarify the requirement for reporting of Adverse Events and Serious Adverse Events, and updated the example of the Serious Adverse Event Form in Appendix F
- Include information on pre-filled syringes as the study will convert from single use vials to pre-filled syringes
- Other minor changes and typographical errors have been corrected throughout

Amendment 3

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study to Determine the Treatment Effect of Denosumab in Subjects with Non-Metastatic Breast Cancer Receiving Aromatase Inhibitor Therapy

Denosumab

Amgen Protocol Number: 20050209

ABCSG Protocol number: ABCSG-18

Amendment Date: 27 November 2012

Rationale:

The primary reason for this amendment is to clarify the definition of post-menopausal status for subjects < 60 years of age. This change will clarify that for subjects < 60 years of age, FSH and estradiol must be in the post-menopausal range and if the subject has had a previous hysterectomy, there is no requirement for a pregnancy test.

The definition of termination date has been updated to a primary analysis data cut-off date (PADCD) and a 1 or 5 year follow-up has been added.

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- Include information on pre-filled syringes as the study will convert from single use vials to pre-filled syringes
- Other minor changes and typographical errors have been corrected throughout

Amendment 3

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study to Determine the Treatment Effect of Denosumab in Subjects with Non-Metastatic Breast Cancer Receiving Aromatase Inhibitor Therapy

Denosumab

Amgen Protocol Number: 20050209

ABCSG Protocol number: ABCSG-18

Amendment Date: 02 November 2012

Rationale:

The primary reason for this amendment is to clarify the definition of post-menopausal status for subjects < 60 years of age. This change will clarify that for subjects < 60 years of age, FSH and estradiol must be in the post-menopausal range and if the subject has had a previous hysterectomy, there is no requirement for a pregnancy test.

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- Other minor changes and typographical errors have been corrected throughout

Amendment 3

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study to Determine the Treatment Effect of Denosumab in Subjects with Non-Metastatic Breast Cancer Receiving Aromatase Inhibitor Therapy

Denosumab

Amgen Protocol Number: 20050209

ABCSG Protocol number: ABCSG-18

Amendment Date: 15 August 2012

Rationale:

The primary reason for this amendment is to clarify the definition of post-menopausal status for subjects < 60 years of age. This change will clarify that for subjects < 60 years of age, FSH and estradiol must be in the post-menopausal range and if the subject has had a previous hysterectomy, there is no requirement for a pregnancy test.

The definition of termination date has been updated to a primary analysis data cut-off date (PADCD) and a 1 or 5 year follow-up has been added.

The investigational product currently being used on this study will expire and the investigational product will be switched from vials to a pre-filled syringe.

Other Changes

In addition the following additional changes are being proposed:

- Clarify eligibility criteria for post-menopausal status
- Clarify the requirement for reporting of Adverse Events and Serious Adverse Events
- Include information on pre-filled syringes as the study will convert from single use vials to pre-filled syringes
- Other minor changes and typographical errors have been corrected throughout

Description of Changes:

The following specific updates have been made to the protocol:

Global Change:

Replace “Amendment 2” with “Amendment 3” and “06 April 2010” with “15 August 2012”

Amendment 2

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study to Determine the Treatment Effect of Denosumab in Subjects with Non-Metastatic Breast Cancer Receiving Aromatase Inhibitor Therapy

Denosumab

Amgen Protocol Number: 20050209

ABCSG Protocol number: ABCSG-18

Amendment Date: 06 April 2010

Rationale:

Sample size calculation

In a phase 3 pivotal study of denosumab compared with placebo in the treatment of women with postmenopausal osteoporosis (Amgen study 20030216), denosumab demonstrated a clinical fracture reduction of 30% compared with placebo (*N Engl J Med* 2009;361:745-55). This result is a reasonable measure by which to predict the clinical fracture rate in the study population in study 20050209 where postmenopausal subjects with breast cancer are being treated with aromatase inhibition that is known for increasing bone turnover.

The originally assumed clinical fracture reduction of 40% by denosumab versus placebo in study 20050209 may be an overestimation and a change to the sample size to adequately power the study for the possibility that the result will be similar is appropriate.

As the hazard ratio has changed from 0.6 to 0.7, the number of events has increased from 128 subjects to 247 subjects. Given the change in hazard ratio and the increase in the study duration the number of subjects to be enrolled has been increased from 2800 to 3400. Based on the recruitment figures to date and the predictions of future recruitment, the overall study duration is estimated to be 96 months, which includes an enrollment period of approximately 71 months.

Interim analysis

The interim analysis will be removed based on the following rationale:

- Since this trial was started in December 2006, new data have emerged from phase 3 studies evaluating denosumab for impact on bone mineral density (BMD) and fracture rate. These studies have demonstrated a consistent and similar improvement in BMD and/or in clinical fracture rate across all study populations (*J Clin Oncol* 2008;26:4875-82; *N Engl J Med* 2009;361:745-55; *N Engl J Med* 2009;361:756-65). Therefore we anticipate that BMD and fracture rate will display a similar effect in this population and consequently the interim analysis is no longer required.
- An independent study specific data monitoring committee will continue to monitor the safety of the subjects on an annual basis.

Reclassification of the Exploratory Endpoints and Secondary Endpoints

Recognizing that registration trials for antiresorptive agents in osteoporosis indications are typically based on a primary endpoint of subject incidence of new vertebral fracture over a 36 months period (N Engl J Med 2009;361:745-55), and also recognizing the clinical importance of recent data about a potential benefit of including intravenous bisphosphonates in the adjuvant treatment for breast cancer on breast cancer – related

endpoints (N Engl J Med 2009;360:679-91), the secondary endpoints were adapted to account for these clinically important outcomes:

- The endpoints "subject incidence of new vertebral fracture at 12 and 24 months", "subject incidence of new vertebral fracture or worsening of pre-existing vertebral fractures", and "change in bone mineral density measurement over a 12 month and 24 month period" were moved to exploratory endpoints and endpoints of "subject incidence of new vertebral fracture over a 36 month period" and "subject incidence of a new or worsening of pre-existing vertebral fractures at month 36" remain as secondary endpoints.
- As the treatment with anti-resorptive agents might have an impact on cancer-related outcomes, the cancer endpoints disease free survival, bone-metastasis free survival, and overall survival have been elevated from exploratory to secondary endpoints.

The primary and secondary null hypothesis will be tested using the hierarchical analysis strategy and the Hochberg procedure to control the overall significance level of 0.05.

Eligibility assessment: DXA scans

The timing of the DXA scan and x-rays for evaluation of inclusion to this study is being increased from 35 days to 120 days.

The current protocol stipulates that DXA scans and x-rays at screening should be performed ≤ 35 days from randomization or ≤ 60 days with approval from the DMC. The timing associated with this inclusion criterion is impacting accrual. Additionally, since BMD declines in this patient population occur over a long period of time and fractures between screening and baseline would occur very infrequently, extending the timeline associated with the screening BMD is not expected to have an impact of the study conduct or study results.

Other Changes

In addition the following additional changes are being proposed:

- The background section has been updated to reflect information available in the most recent version of the Investigator's Brochure
- The protocol refers to the analysis at 36 Months/End of Study. The term "End of Study" was removed as the 36 month visit will be associated with the time period it falls into rather then being directly associated with End of Study visit
- The end of study and termination date have been clarified throughout
- The location of the clinical sites has been generalized to include sites outside of Austria
- The consent form has been separated from the protocol so that up-dates on the consent will not require amending the protocol
- The data management system had been specified as InTrial™ in the protocol and is currently being replaced with MACRO.
- Other minor changes and typographical errors have been corrected throughout

Amendment 1

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study to Determine the Treatment Effect of Denosumab in Subjects with Non-Metastatic Breast Cancer Receiving Aromatase Inhibitor Therapy

Amgen Protocol Number *20050209*
ABCSG-18

Amendment Date: 12 June 2006

Rationale:

Protocol 20050209/ABCSG-18 is being amended for three reasons:

1. Eligibility assessment: Bone Scans, DXA scans and X-rays.

   The current protocol stipulates that all screening procedures should be performed ≤35 days from randomization. The ABCSG has noted that for many patients these radiological assessments may have recently been performed as part of their routine clinical care. Repeating these procedures unnecessarily would increase the radiation exposure to patients with no added clinical benefit. In the case of the bone scan, it is regarded as clinically acceptable to include scans that have been performed within the last 6 months to determine any evidence of metastasis.
   With respect to the DXA scans and X-rays, it is intended that wherever possible they are performed within the 35 day screening window. However, if there are appropriate DXA scans and/or X-ray films available within a 60 day window from the date of randomization, then the validity of these results will be assessed on a case by case basis by the Data Monitoring Committee who will review their suitability as part of a patient's eligibility to participate in the trial.

2. Change to Patient Information Sheet
   Due to emerging data from the ongoing osteoporosis program with Denosumab, the following paragraph is being added to patient information sheets:

   "The effect of denosumab regarding your bone density is reversible and a discontinuation of denosumab may lead to a loss in gained bone density. After discontinuation, your BMD-Scores should be followed carefully with regard to a possible loss of mineral density. Ask your physician for alternative treatments which can maintain your gained BMD".

3. DXA scan procedures
   Section 7.9.2 of the protocol contains a misleading paragraph regarding the use of standard phantoms on DXA machines. Each type of DXA machine needs to be calibrated daily in accordance with the manufacturer's guidelines and in line with the institution's policy. The paragraph referring to the scanning of standard

phantoms has therefore been removed from the protocol to avoid both ambiguity and confusion.

Description of Changes (all changes to the protocol are indicated in bold text):

Changes to Protocol in Connection with Point 1:

Page: 31

Section: 7.1 Screening Visit

Entire paragraph

Replace:

All screening procedures must be completed ≤ 35 days before the day of randomization.

With:

With the following exceptions, all screening procedures must be completed ≤ 35 days before the day of randomization.
For eligibility purposes, all subjects must have a bone scan that that has been performed within 6 months of randomization.
DXA and X-rays should be performed within the 35 day screening window. However, if appropriate DXA and/or X-ray assessments have been performed within 60 days of randomization, the Data Monitoring Committee will assess whether they are suitable for determining the subject's eligibility or whether the radiological assessments need to be repeated within the 35 day screening window.

Page: 64 (table) and 65 (legend)

Section: Appendix A – Schedule of Assessments

Inclusion of symbols within the "Screening Period" column of the table:

¤ denotes X-rays and DXA screening assessments

§ denotes bone scan screening assessment

Add: At the bottom of the legend, on page 65, the following text has been inserted:

- ¤ **X-rays and DXA assessments performed ≤60 days of randomization but outside the 35 day screening window will be assessed by the Data Monitoring Committee for determining a subject's eligibility.**
- **§** **A bone scan performed ≤ 6 months of date of randomization will be considered as valid for the purposes of assessing a subject's eligibility.**