Title: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Safety and Efficacy of Denosumab in Pediatric Subjects With Glucocorticoid-induced Osteoporosis

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Clinical Study Sponsor: Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Telephone: +1-805-447-1000

Key Sponsor Contact(s): [redacted], MD
Clinical Research Medical Director
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Telephone: [redacted]
Email: [redacted]

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Amendment 4	**10 July 2023**

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).

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Investigator's Agreement

I have read the attached protocol entitled A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Safety and Efficacy of Denosumab in Pediatric Subjects With Glucocorticoid-induced Osteoporosis, dated **10 July 2023**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

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

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

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

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Safety and Efficacy of Denosumab in Pediatric Subjects With Glucocorticoid-induced Osteoporosis

Study Phase: 3

Indication: Glucocorticoid-induced Osteoporosis

Primary Objective: To evaluate the effect of denosumab on lumbar spine bone mineral density (BMD) Z-score as assessed by dual-energy X-ray absorptiometry (DXA) at 12 months in children 5 to 17 years of age with Glucocorticoid (GC)-induced osteoporosis (GiOP).

Secondary Objective(s): To evaluate the effect of denosumab in children 5 to 17 years of age with GiOP with respect to:

- Change in lumbar spine BMD Z-score as assessed by DXA from baseline to 6, 18, 24, and 36 months
- Change in proximal femur BMD Z-score as assessed by DXA from baseline to 6, 12, 18, 24, and 36 months
- Incidence of X-ray confirmed long-bone fractures and new and worsening vertebral fractures **during** 12, 24, and 36 months
- Incidence of improving vertebral fractures at 12, 24, and 36 months **compared to baseline**
- Incidence of **new** and **worsening** vertebral and nonvertebral fractures **during** 12, 24, and 36 months
- Change in Childhood Health Questionnaire – Parent Form-50 (CHQ-PF-50) Physical Summary Score at 12, 24, and 36 months
- Change in CHQ-PF-50 Psychological Summary Score at 12, 24, and 36 months
- Change in Childhood Health Assessment Questionnaire (CHAQ) Disability Index Score at 12, 24, and 36 months
- Change in Wong-Baker Faces Pain Rating Scale (WBFPRS) at 12, 24, and 36 months
- Change in growth velocity, determined by calculating age-adjusted Z-scores for height, weight, and body mass index (BMI), at 12, 24, and 36 months
- Serum concentration of denosumab at 1 and 10 days, and 6, 12, and 18 months (additional serum denosumab pharmacokinetics [PK] samples to be collected at day 30 and month 3 in a PK/[redacted]substudy of up to 15 subjects)

Hypotheses: The hypothesis of this study is that the change from baseline in lumbar spine BMD Z-score following 12 months of denosumab treatment in children 5 to 17 years of age with GiOP will be greater than placebo.

Primary Endpoint: Change from baseline in lumbar spine BMD Z-score as assessed by DXA at 12 months

Secondary Endpoint(s):

- Change from baseline in lumbar spine BMD Z-score as assessed by DXA at 6, 18, 24, and 36 months
- Change from baseline in proximal femur BMD Z-score as assessed by DXA at 6, 12, 18, 24, and 36 months
- Subject incidence of X-ray confirmed long-bone fractures and new and worsening vertebral fractures **during** 12, 24, and 36 months
- Subject incidence of improving vertebral fractures at 12, 24, and 36 months compared to **baseline**

- Subject incidence of **new** and **worsening** vertebral and nonvertebral fractures **during** 12, 24, and 36 months
- Change from baseline in CHQ-PF-50 Physical Summary Score at 12, 24, and 36 months
- Change from baseline in CHQ-PF-50 Psychological Summary Score at 12, 24, and 36 months
- Change from baseline in CHAQ Disability Index Score at 12, 24, and 36 months
- Change from baseline WBFPRS at 12, 24, and 36 months
- Change from baseline in growth velocity, determined by calculating age-adjusted Z-scores for height, weight, and BMI, at 12, 24, and 36 months
- Serum concentration of denosumab at 1, 10, and 30 days, and 3, 6, 12, and 18 months

Exploratory Endpoint(s):

[redacted]

Study Design: This is a phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel group study in pediatric subjects, age 5 to 17 years, with GiOP. Twenty-four subjects including at least 16 evaluable subjects for the primary analysis will be enrolled. Subjects will be randomized in a 2:1 (active:placebo) allocation ratio to receive either denosumab 1 mg/kg body weight (BW) (up to a maximum of 60 mg) subcutaneous (SC) every 6 months (Q6M) or matching placebo SC Q6M. Up to 15 subjects at selected sites will be given the opportunity to participate in a PK/[redacted] substudy. The study is comprised of 2 periods, a 24-month treatment period (including a 12-month placebo-controlled period and a 12-month open-label period) and a 12-month off-treatment observation period. At the end of the first 12 months of the placebo-controlled treatment period, all subjects will receive open-label denosumab Q6M for 12 months. Upon completion of the 24-month treatment period, the 12-month observation period will begin. Daily supplements of calcium and vitamin D will be given to all subjects during the 24-month treatment period. Daily supplements of calcium and vitamin D may also be given to subjects during the 12-month observation period, if deemed medically warranted by the investigator. The planned length of participation in the study for an individual subject is approximately 3 years, which includes screening (up to 35 days), treatment phase (24 months), and off-treatment observation period (12 months). The anticipated dropout rate is approximately 10% in the first year.

Treatment Period

The treatment period will last for 24 months including 12-month double-blind and 12-month open-label treatment. During the first 12 months of the treatment period, subjects will receive either denosumab 1 mg/kg BW (up to a maximum of 60 mg) SC Q6M or matching placebo SC Q6M. At the end of the first 12 months of the treatment period, all subjects will receive open-label denosumab Q6M for 12 months. The last dose of study medication will be administered at month 18.

Observation Period

The observation period will start immediately after the 24-month treatment period and last 12 months, during which study subjects will receive no investigational product. Study subjects are to be followed up during the 12-month observation period according to the following guidelines:

- Subjects who are currently on systemic GC for the treatment of the underlying non-malignant condition(s) at the month 24 visit should discontinue investigational product and transition to another osteoporosis treatment per local standard of care, according to the medical judgment of the investigator, for an additional 12 months or until systemic GC treatment is discontinued (see Section 2.3.6)
- Subjects who are no longer on systemic GC for the treatment of the underlying non-malignant condition(s) at the month 24 visit should discontinue investigational product and be followed up for an additional 12 months off treatment; however, subjects who, during the 12-month observation period, resume systemic GC therapy, experience a worsening of their osteoporosis, or require osteoporosis therapy based on the medical judgment of the investigator may resume osteoporosis treatment per local standard of care at the discretion of the investigator

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Sample Size: A total of 24 subjects will be randomized into the study (approximately 16 to denosumab and 8 to placebo).

Summary of Subject Eligibility Criteria:

Inclusion criteria will include the following:

- Subject's legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated
- Male or female subjects, age 5 to 17 years, inclusive, at the time of informed consent.
- Clinical diagnosis of GiOP as defined by the following (and consistent with the International Society for Clinical Densitometry definition of osteoporosis in children and adolescents [Bishop et al, 2014])
  - A confirmed diagnosis of non-malignant condition(s) requiring treatment with systemic GC (including, but not limited to, chronic rheumatologic, gastrointestinal, neurologic, respiratory, and/or nephrological conditions)
    - Subjects who are on systemic GC only as replacement therapy for adrenal insufficiency are not eligible for the study
  - Treatment with systemic GC (intravenous or oral) of any duration for the underlying non-malignant condition(s) within the 12 months prior to screening
    - Prepubertal children should be expected to require significant GC use during the study, per investigator opinion
  - Evidence of at least 1 vertebral compression fracture of Genant grade 1 or higher, as assessed by the central imaging vendor on lateral spine X-rays performed at screening or within 2 months prior to screening; or, in the absence of vertebral compression fractures, presence of both clinically significant fracture history (ie, $\geq$ 2 long-bone fractures by age 10 years or $\geq$ 3 long-bone fractures at any age up to 17 years) and lumbar spine BMD Z-score $\leq$ -2.0, as assessed by the central imaging vendor

Exclusion criteria will include the following:

- Current hyperthyroidism (unless well controlled on stable antithyroid therapy)
- Current clinical hypothyroidism (unless well controlled on stable thyroid replacement therapy)
- History of hyperparathyroidism
- Current hypoparathyroidism
- Any causes of primary or secondary osteoporosis (other than GC use), or previous exposure to non-GC medications, which the investigator considers to have been a major factor contributing to the patient's fracture(s)

- Current adrenal insufficiency as the sole indication for GC therapy
- Duchenne muscular dystrophy with symptomatic cardiac abnormality
- Current malabsorption (in children with serum albumin < lower limit of normal [LLN], malabsorption should be clinically ruled out by the investigator to confirm eligibility)
- Known intolerance to calcium or vitamin D supplements
- Active infection or history of infections, defined as follows:
  - Any active infection for which systemic anti-infectives were used within 4 weeks prior to screening
  - Serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to screening
  - Recurrent or chronic infection or other active infection that, in the opinion of the investigator, might compromise the safety of the subject
- History of malignancy
- History of any solid organ or bone marrow transplant
- Evidence of untreated oral cavities or oral infections
- Recent or planned invasive dental procedure
- Surgical tooth extraction which has not healed by screening
- Currently unhealed fracture or osteotomy, as defined by orthopedic opinion
- Osteotomy within 5 months prior to screening
- Spinal fusion surgery within 5 months prior to screening or not yet healed (per orthopedic surgeon)
- Rodding surgery within 5 months prior to screening or not yet healed (per orthopedic surgeon)
- Anticipated major skeletal surgery (eg, rodding surgery, spinal surgery) within the next 12 months from day 1
- Planned orthopedic surgery that, in the opinion of the investigator, would require missing any dose of investigational product in year 1 or 2 or more doses thereafter
- History of rare hereditary problems of fructose intolerance
- History of long QT syndrome
- History of alcohol or drug abuse
- History or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion
- Serum albumin-corrected calcium < LLN or > 10% above upper limit of normal (ULN) at screening
- Serum vitamin D < 20 ng/mL at screening (rescreening for vitamin D level < 20 ng/mL will be allowed, after adequate supplementation)
- Serum phosphorus < LLN at screening
- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 1.5 x ULN (or > 5 x ULN in subjects with dystrophinopathies) at screening (see Section 4.1.2 for further details)

In subjects with dystrophinopathies, AST or ALT elevation > 5 x ULN may not be exclusionary if

- It is associated with serum creatine phosphokinase (CPK) elevation

  AND
- Serum total bilirubin, alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), and prothrombin time/international normalized ratio (PT/INR) are < ULN, and serum albumin is > LLN

  AND
- There are no symptoms or signs of hepatic inflammation, such as nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, with no other immediately apparent possible cause (eg, gastroenteritis or constipation)

- Serum total bilirubin > 1.5 x ULN at screening (subjects with Gilbert syndrome are eligible)
- Positive blood screen for human immunodeficiency virus (HIV)-1 or -2 antibody
- Positive blood screen for hepatitis B surface antigen or hepatitis C antibody
- Estimated glomerular filtration rate < 60 mL/min/1.73 m^2 at screening (calculated by the bedside Schwartz equation)
- Less than 2 evaluable vertebrae by DXA evaluation in the region of interest L1-L4, as confirmed by the central imaging laboratory
- Prior treatment for bone disease with any of the following at any time:
  - Denosumab
  - Strontium
  - Fluoride
- Recent Bisphosphonate (BP) treatment, according to the following guidelines:
  - Zoledronic acid (ZA) within 6 months prior to screening (subjects are eligible if 6 months will have elapsed, since the previous ZA dose, by the time of first dose of investigational product)
  - Oral BP or intravenous BP (other than ZA), if the first dose of investigational product would be before their next scheduled BP dose (subjects are eligible if at least 1 BP dosing interval will have elapsed at time of the first dose of investigational product)
- Administration of any of the following treatment within 3 months prior to screening:
  - Growth hormone (unless on stable dose for at least 3 months prior to screening)
  - Calcitonin
  - Cathepsin K inhibitor
  - Other bone active drugs including anti-convulsants (except gabapentin and benzodiazepines) and heparin
  - Chronic systemic ketoconazole, androgens (except subjects who have received testosterone therapy for physiologic replacement in the setting of documented hormonal deficiency), cinacalcet, aluminum, lithium, protease inhibitors, gonadotropin releasing hormone agonists
- Initiation of any of the following biologic agents within 4 weeks prior to screening:
  - Anti-alpha 4 integrin antibody (eg, natalizumab)
  - Anti-CD4/CD8 T-cells (eg, alefacept)
  - Anti-IL-12/IL-23 (eg, ustekinumab)

  - CTLA4 inhibitor (eg, abatacept)
  - IL1 receptor antagonist (eg, anakinra)
  - IL6 inhibitor (eg, tocilizumab)
  - Monoclonal antibody to CD20 (eg, rituximab)
  - Tumor necrosis factor antagonist (eg, adalimumab, certolizumab, golimumab, etanercept, infliximab)
- Current treatment with > 1 biologic agent for underlying inflammatory disease
- Currently pregnant or planning a pregnancy during the study and for an additional 5 months after the last dose of investigational product
- Currently breastfeeding or planning on breastfeeding during the study and for an additional 5 months after the last dose of investigational product
- For sexually active girls: refusal to use highly effective methods of contraception and to continue this practice for 5 months after the last injection of investigational product
- Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge
- Subject's parent or legal representative has any kind of disorder that, in the opinion of the investigator, may compromise the ability to give written parental permission for informed consent
- Currently receiving treatment in another investigational device or drug study, or < 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded

For a full list of eligibility criteria, please refer to Section 4.1.1 and Section 4.1.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: Subjects will be randomized to receive denosumab or placebo every 6 months in a 2:1 allocation ratio for the first 12 months. At the end of the initial 12-month period, all subjects will receive open-label denosumab Q6M for a further 12 months. All subjects will receive investigational product through month 18. Denosumab will be administered at a dose of 1 mg/kg BW (up to a maximum of 60 mg).

Denosumab and placebo will be manufactured and packaged by Amgen Inc. Denosumab will be presented as a 70 mg/mL solution containing 1.7 mL in a 3 mL vial. Placebo will be presented as a solution identical in appearance to denosumab, without the active ingredient. All subjects will receive a SC injection of investigational product every 6 months for 24 months (last injection to be administered at month 18). All SC injections must be administered by authorized site personnel. The injection should not be administered in the same arm from which blood is drawn. Investigational product should be administered only after all other study visit procedures have been completed. If a subject misses a scheduled dose of denosumab during a study visit, then he/she should return to the clinic to receive the missed dose within the visit window allowed for that particular visit. The clinical monitor should be contacted for specific instructions if a subject cannot receive his/her dose within the allowed visit window.

Procedures: Key procedures for this study involve various imaging techniques. Bone densitometry assessments of the lumbar spine and proximal femur performed by DXA, lateral radiographs of the thoracic and lumbar spine, anteroposterior (AP) radiographs of both knees (to calculate the metaphyseal index Z-score of each knee), and dental radiographs will be used to assess GiOP in this pediatric population. Subjects will also undergo a visual inspection of the oral cavity to look for the presence of unerupted molars.

Several instruments will be used to assess the subject's health-related quality of life, physical functioning, and pain intensity: the CHQ-PF-50, CHAQ, and the WBFPRS.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 2).

Statistical Considerations:

Sample Size Considerations:

The study will enroll 24 subjects. Assuming that approximately 10% of subjects will not be evaluable at month 12 for the primary efficacy endpoint due to dropout, the analysis set for the primary efficacy endpoint will include approximately 20 subjects.

Analyses:

The primary analysis will be conducted at the time of the final analysis. The final analysis for the study, including the analysis of the primary endpoint, will be performed when all enrolled subjects have had the opportunity to complete the 36-month follow-up.

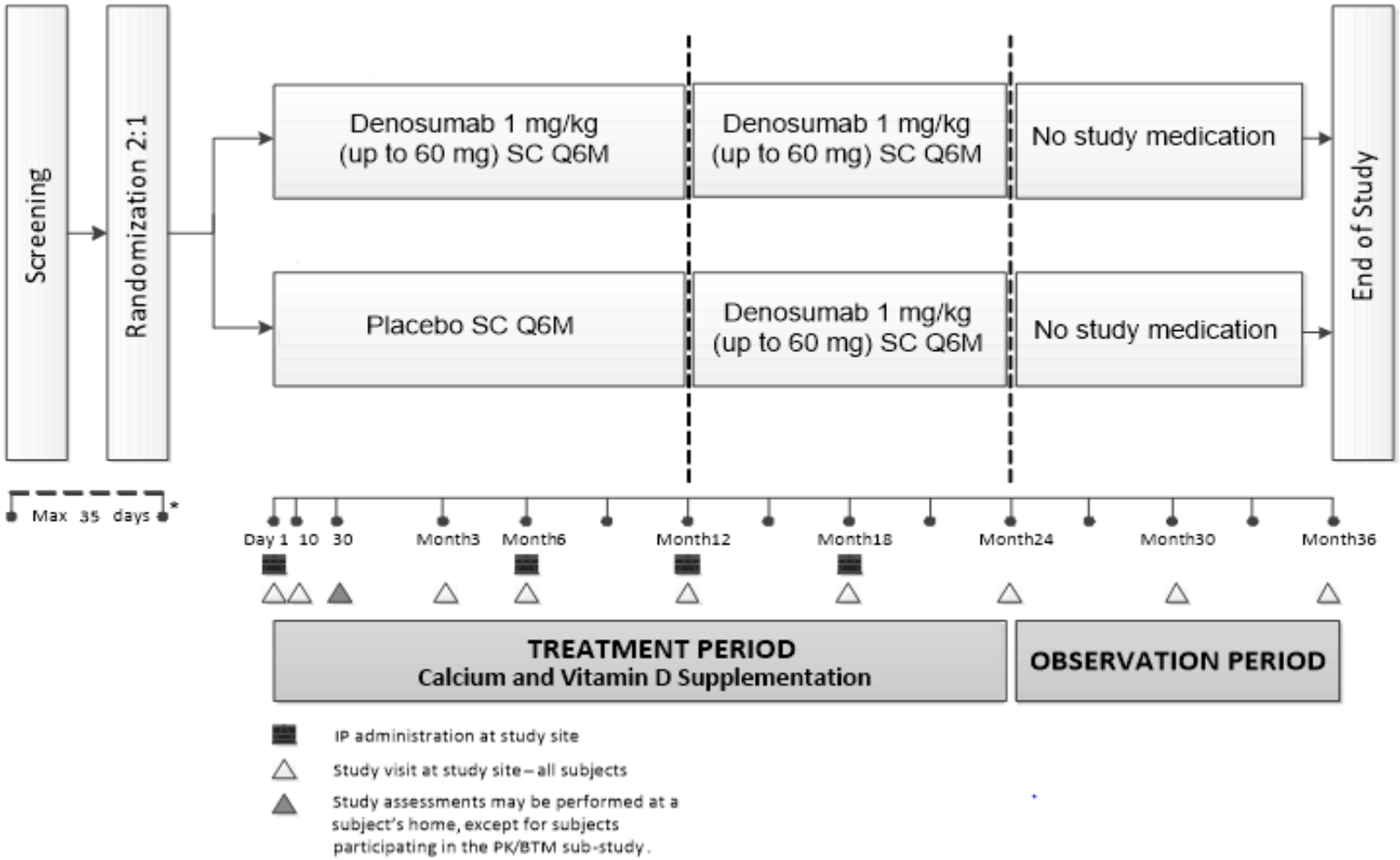
The primary efficacy endpoint will be the change from baseline in lumbar spine BMD Z-score at 12 months and will be analyzed based on the primary DXA analysis set using an analysis of covariance (ANCOVA) model including treatment (denosumab vs placebo), baseline age (age at informed consent), and baseline BMD Z-score. Missing baseline and postbaseline BMD Z-scores will not be imputed. The superiority of denosumab compared to placebo for the primary efficacy endpoint will be estimated from the 12-month least-squares (LS) mean of the treatment difference (denosumab – placebo) and the corresponding 95% confidence interval.

For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen Inc.

Data Element Standards Version(s)/Date(s):	Version(s) 5: 20 March 2015

Study Design and Treatment Schema



* In the event of rescreening, an additional 42 days will be allowed.

Study Glossary

Abbreviation or Term	Definition/Explanation
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AP	Anteroposterior
AST	Aspartate aminotransferase
BMD	Bone mineral density
BMI	Body mass index
BP	Bisphosphonate
[redacted]	[redacted]
BW	Body weight
CHAQ	Childhood Health Assessment Questionnaire
CHQ-PF-50	Childhood Health Questionnaire – Parent Form-50
CPK	Creatine phosphokinase
CPRD	Clinical Practice Research Datalink
CRF	Case report form
DILI	Drug-induced liver injury
DMC	**Data Monitoring Committee**
DXA	Dual-energy X-ray absorptiometry
EDC	Electronic data capture
Electronic Source Data (eSource)	Source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a study
End of Follow-up	Defined as when the last subject completes the last protocol-specified assessment in the study
End of Study (end of trial)	Defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Study (primary completion)	Defined as the date when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s), If there are multiple primary endpoint(s) this would be the date of last primary endpoint assessment.
End of Study for Individual Subject	Defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Treatment	Defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
eSAE	electronic Serious Adverse Event
Exposure-Response Analysis	Mechanism-based modeling and simulation and statistical analyses based on individual PK exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamic effects, efficacy and safety endpoints
FAS	Full analysis set
GC	Glucocorticoid

Abbreviation or Term	Definition/Explanation
GCP	Good Clinical Practice

Abbreviation or Term	Definition/Explanation
GGT	Gamma-glutamyltransferase
GiOP	Glucocorticoid-induced osteoporosis
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
ICF	Informed consent form
ICH	International Conference for Harmonisation
IEC	Independent ethics committee
INR	International normalized ratio
IVR	Interactive Voice Response – telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
IWR	Interactive Web Response – web-based technology that is linked to a central computer in real time as an interface to collect and process information.
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
LLN	Lower limit of normal
LS	Least-squares
PK	Pharmacokinetic
PT	Prothrombin time
Q3M	**Every 3 months**
Q6M	Every 6 months
RANK	Receptor activator of nuclear factor kappa
RANKL	Receptor activator of nuclear factor kappa-B ligand
SC	Subcutaneous
[redacted]	
Source Data	Information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies) (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	Defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	Total bilirubin
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WBFPRS	Wong-Baker Faces Pain Rating Scale

Abbreviation or Term	Definition/Explanation
ZA	Zoledronic acid

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1. OBJECTIVES

1.1 Primary

To evaluate the effect of denosumab on lumbar spine bone mineral density (BMD) Z-score as assessed by dual-energy X-ray absorptiometry (DXA) at 12 months in children 5 to 17 years of age with glucocorticoid (GC)-induced osteoporosis (GiOP).

1.2 Secondary

To evaluate the effect of denosumab in children 5 to 17 years of age with GiOP with respect to:

- Change in lumbar spine BMD Z-score as assessed by DXA from baseline to 6, 18, 24, and 36 months
- Change in proximal femur BMD Z-score as assessed by DXA from baseline to 6, 12, 18, 24, and 36 months
- Incidence of X-ray confirmed long-bone fractures and new and worsening vertebral fractures **during** 12, 24, and 36 months
- Incidence of improving vertebral fractures at 12, 24, and 36 months **compared to baseline**
- Incidence of **new** and **worsening** vertebral and nonvertebral fractures **during** 12, 24, and 36 months
- Change in Childhood Health Questionnaire – Parent Form-50 (CHQ-PF-50) Physical Summary Score at 12, 24, and 36 months
- Change in CHQ-PF-50 Psychological Summary Score at 12, 24, and 36 months
- Change in Childhood Health Assessment Questionnaire (CHAQ) Disability Index Score at 12, 24, and 36 months
- Change in Wong-Baker Faces Pain Rating Scale (WBFPRS) at 12, 24, and 36 months
- Change in growth velocity, determined by calculating age-adjusted Z-scores for height, weight, and body mass index (BMI), at 12, 24, and 36 months
- Serum concentration of denosumab at 1 and 10 days, and 6, 12, and 18 months (additional serum denosumab pharmacokinetics [PK] samples to be collected at day 30 and month 3 in a PK [redacted] substudy of up to 15 subjects)

1.3 Safety

To evaluate the effect of denosumab in children 5 to 17 years of age with GiOP with respect to:

- Adverse events and serious adverse events
- Laboratory parameters
- Vital signs
- Antidenosumab antibodies

1.4 Exploratory

[redacted]

2. BACKGROUND AND RATIONALE

2.1 Disease

Glucocorticoid (GC)-induced osteoporosis (GiOP) is the most common condition of medication-induced bone loss in children (Ward et al, 2010). Glucocorticoid -induced osteoporosis is the result of profound effects of GCs on bone cells, which include inhibition of osteoblastogenesis and promotion of osteoblast apoptosis, resulting in significant reductions in bone formation, as well as increase in osteoclast-mediated bone resorption (Leonard, 2007; Ward, 2005; Canalis et al, 2004; Bianchi, 2002; Weinstein et al, 1998). Decreased BMD has been described in various pediatric disorders that require GCs, such as asthma, juvenile rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and organ transplantation (Burnham and Leonard, 2004; Daniels et al, 2003; Leonard and Zemel, 2002; Boot et al, 1997). Some of the detrimental bone effects attributed to GCs may be caused by the underlying inflammatory disease being treated with GCs. Inflammatory cytokines, such as tumor necrosis factor-α, known to be increased in rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease, suppress bone formation and promote bone resorption (Parfitt et al, 1996). The GC-induced decrease in bone mass is associated with an increase in fracture risk. A population-based study reported increased fracture risk (adjusted odds ratio: 1.32; 95% confidence interval: 1.03, 1.69) in children who required $>$ 4 courses of glucocorticoids (van Staa et al, 2003).

There are currently no widely accepted guidelines for or approaches to the treatment of osteoporosis in the pediatric population. Bisphosphonates (BP) are not licensed for the treatment of osteoporosis in children, but they have been evaluated in exploratory clinical studies in the setting of childhood osteoporosis. Most BP studies in pediatric GiOP have shown significant increases in either BMD Z-scores (Inoue et al, 2008; Acott et al, 2005) or lumbar spine BMD (Simm et al, 2011; Bianchi et al, 2000).

However, based on a 2010 Cochrane review, there is not sufficient evidence to support BP use as standard therapy for pediatric GiOP (Ward et al, 2010). Thus, an unmet need remains in children with GiOP.

2.2 Amgen Investigational Product Background

Denosumab is a fully human monoclonal antibody that binds with high affinity and specificity to and neutralizes the activity of the receptor activator of nuclear factor kappa- B ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Denosumab is currently indicated for the treatment of postmenopausal women with osteoporosis, treatment of men with osteoporosis, treatment of bone loss in men receiving androgen deprivation therapy for prostate cancer, and treatment of bone loss in women receiving aromatase inhibitor therapy for breast cancer.

2.3 Pediatric Risk Assessment

This pediatric study involves greater than minimal risk, but presents the prospect of direct benefit to the subject. Pediatric subjects treated with denosumab in this study are expected to have a risk profile comparable to that observed in adults. Additional information on specific risks in this pediatric population is provided in Sections 2.3.1 through 2.3.6. The extensive denosumab clinical development program includes pivotal phase 3 studies in bone loss settings in adults, ie postmenopausal women with osteoporosis (Study 20030216) or low bone mass (Study 20040132); bone loss associated with androgen deprivation therapy for prostate cancer (Study 20040138) or aromatase inhibitor therapy for breast cancer (Study 20040135); men with osteoporosis (Study 20080098), and in adult subjects with GiOP (Study 20101217 [Saag et al, 2018]). There is an ongoing study in pediatric subjects with osteogenesis imperfecta (Study 20130173). In addition, denosumab has been studied in adolescent subjects with giant cell tumor of bone at a dose of 120 mg every 4 weeks (Study 20062004).

In clinical studies to date, there has been a comparable incidence of adverse events overall between the denosumab and placebo or active-comparator treatment groups and a low incidence of treatment-related adverse events, serious adverse events, withdrawals due to adverse events, and deaths. Most adverse events have been mild to moderate in severity, transient, and considered unrelated to denosumab. Adverse reactions to denosumab include hypocalcemia; hypersensitivity; skin infections, predominantly cellulitis, leading to hospitalization; osteonecrosis of the jaw; atypical femoral fracture; eczema (including dermatitis, allergic dermatitis, atopic dermatitis, and

contact dermatitis); cataracts in males with prostate cancer receiving androgen deprivation therapy; pain in the extremities; and musculoskeletal pain. Multiple vertebral fractures and hypercalcemia may occur following discontinuation of denosumab treatment.

In the bone loss setting, denosumab use is contraindicated in pregnancy, in patients with hypocalcemia, and in patients with hypersensitivity to the active substance or to any of the excipients.

Volumes of blood withdrawn for analysis in association with clinical monitoring will be minimized as appropriate for this pediatric population based on body weight (BW) (European Union Ethical Considerations, 2008).

2.3.1 Hypocalcemia

Skeletal turnover rates vary by age and are higher in children than adults. These higher bone turnover rates expected at baseline in children may increase the risk for hypocalcemia and hypophosphatemia resulting from denosumab-mediated reduction of bone turnover. In addition, recent clinical reports of denosumab administration in pediatric patients with disorders of high bone turnover (eg, fibrous dysplasia and juvenile Paget's disease) have described disturbances in mineral metabolism, including hypocalcemia and hypophosphatemia (Grasemann et al, 2013; Boyce et al, 2012).

To minimize such risk, the following strategies will be employed:

- Calcium and vitamin D supplementation will be given to all study subjects
- Serum calcium and phosphorus concentrations will be monitored throughout the study on a regular basis
- Subjects will not be eligible to participate if they have evidence of hypocalcemia; diseases that increase the risk of hypocalcemia, including, but not limited to, malabsorption and chronic kidney disease (as defined by an estimated glomerular filtration rate < 60 mL/min/1.73 m^2); or additional risk factors for detrimental effects of hypocalcemia, eg, a history of long QT syndrome
- Occurrence of severe or symptomatic hypocalcemia will prompt discontinuation of study medication and institution of appropriate medical treatment

2.3.2 Hypercalcemia in Pediatric Subjects Receiving Denosumab and After Discontinuation of Denosumab

In the **clinical trial and** postmarketing setting, clinically significant cases of hypercalcemia requiring hospitalization have been observed in patients, including those with developing skeletons, **at the end of every 3 months (Q3M) dosing period or in those** who had previously received off-label denosumab. These incidents of

hypercalcemia have presented with severe vomiting with or without acute renal failure, and have occurred in patients who had used denosumab at higher doses and/or frequencies than those being used by the patient population in this study. **In pediatric patients with osteogenesis imperfecta**, **severe life-threatening adverse events of hypercalcemia have been reported at or near the end of the denosumab 1 mg/kg Q3M dosing period (> 60 days from the previous dose) in Study 20130173.** In ongoing XGEVA Study 20062004 (in subjects with giant cell tumor of bone), a 19-year-old subject developed clinically significant hypercalcemia approximately 8 months after the discontinuation of XGEVA dosing (denosumab 120 mg every 4 weeks). Therefore, **hypercalcemia**, **including** off-treatment hypercalcemia, is a potential risk in this pediatric population receiving Prolia®.

2.3.3 Osteopetrosis

In children, osteoclast activity is necessary to remove the cartilaginous anlagen of bone. Genetic deficiency in RANKL leads to osteopetrosis, a disorder of poor bone quality, retained cartilage, frequent fractures, and a high bone mass typified by poorly modelled bones with widened, club-shaped metaphyses. Significant reduction of this resorption-based modeling can lead to osteopetrosis-like changes with a similar abnormal geometry (Whyte et al, 2003). In nonclinical studies of denosumab, the severity of phenotypic changes observed in the growth plate and bone was consistent with the rate of longitudinal growth in the bone, with limited and reversible effects in the adolescent monkey. The most rapid increase in stature in humans occurs during the first 9 or 12 months of life, and head circumference continues to increase sharply over the first 2 years of life (Centers for Disease Control and Prevention, 2011). Based on these data, the potential for significant alterations of skeletal growth and morphology is lower in children $\geq$ 5 years of age, who will be enrolled in this study. The limited and reversible bone effects of denosumab in the adolescent monkey (the second most rapid growth phase), lack of negative biomechanical consequences seen in the infant mice, and the radiographic monitorability minimize the risk of denosumab administration in pediatric patients whose growth rates approximate that of adolescent monkeys.

Strategies to assess changes to the skeleton include the following:

- Physical examination and radiographic assessments will be performed on a regular basis throughout the study to monitor for possible detrimental skeletal changes; such assessment will also include evaluation of metaphyseal index via knee X-ray to be performed every 6 months throughout the study in subjects with open growth plates only, as only in subjects with open growth plates does the potential risk exist of an abnormal rate of increase in metaphyseal width

- Changes in growth plate morphology as observed in the 6 months monitoring considered by the investigator to be unexpected and having an adverse clinical impact for the subject during the study will prompt discontinuation of study medication and institution of appropriate follow-up

2.3.4 Tooth Eruption

RANKL plays an important role in tooth eruption. In non-clinical studies conducted in neonatal rats, osteoprotegerin-immunoglobulin Fc segment complex and alendronate administration impaired the eruption of second and third molars and also reduced incisor growth. These findings were at least partially reversible within 10 weeks of discontinuing osteoprotegerin-immunoglobulin Fc segment complex. In infant monkeys exposed in utero to denosumab, there was no effect on tooth eruption, although altered bone shape and jaw length led to tooth dysplasia and malalignment. Such findings were not observed in adolescent cynomolgus monkeys. These data suggest that the use of denosumab in the rapidly growing skeleton carries potential risk for impaired tooth eruption.

To minimize this risk, molar eruption and mandibular shaping will be monitored using visual inspection and X-ray assessments.

2.3.5 Serious Infections

RANKL is expressed on activated T and B lymphocytes and in lymph nodes. Therefore, RANKL inhibition may theoretically increase the risk of infection. In a clinical trial of over 7800 women with postmenopausal osteoporosis, the overall incidence of infections, including opportunistic infections, was similar between the denosumab and placebo groups. However, serious skin infections leading to hospitalization were reported more frequently in the denosumab group than in the placebo group. Subjects on concomitant immunosuppressant agents, such as GCs, may be at increased risk of serious infections.

While the completed clinical study of denosumab in adult GiOP (Study 20101217 [Saag et al, 2018]) has not shown an excess risk for serious infection associated with denosumab use, strategies have been implemented in this pediatric study to minimize the risk for serious infections and include the following:

- Subjects who have initiated a biologic agent for the treatment of underlying inflammatory disease < 4 weeks prior to screening or are on > 1 biologic agent for the treatment of underlying inflammatory disease will not be eligible for study participation
- Any subject who develops a serious opportunistic infection will permanently discontinue study medication

- Any subject who develops a serious infection during the study and is receiving a biologic agent for the treatment of underlying inflammatory disease will permanently discontinue study medication

2.3.6 Multiple Vertebral Fractures Following Treatment Discontinuation

Multiple vertebral fractures may occur following discontinuation of denosumab treatment, particularly in subjects with a history of vertebral fracture. Among postmenopausal women with osteroporosis who discontinued denosumab during the placebo-controlled FREEDOM trial and its open-label active-treatment extension, the incidence of new vertebral fracture was higher than in subjects who remained on treatment, but similar to the incidence in subjects who discontinued placebo, ie, had never been treated. Among subjects who experienced off-treatment new vertebral fractures, a greater percentage of those who discontinued denosumab than placebo sustained multiple new vertebral fractures. Prior vertebral fracture before or during treatment was the strongest predictor of off-treatment new vertebral fracture, including multiple vertebral fractures.

The current study includes a 12-month off-treatment observation period following the 24-month treatment period. The intent of the observational period was to evaluate clinical outcomes after investigational product discontinuation. Discontinuation of osteoporosis treatment for subjects who continue to administer systemic GCs for the underlying non-malignant condition(s) at the end of the treatment period may be inconsistent with standard of care, particularly as subjects were required to have a clinically significant fracture history to participate.

With the identified risk for multiple vertebral fractures after denosumab cessation in a setting where study subjects are at high risk for fracture, the mandated observation period will be managed as follows: to minimize the risk of multiple vertebral fractures following treatment discontinuation, subjects who currently are administering systemic GC therapy for the underlying non-malignant condition(s) upon completing the 24-month treatment period should transition to osteoporosis treatment per local standard of care for an additional 12 months or until systemic GC treatment is discontinued. Local standard of care for pediatric subjects with GiOP may include BP use. It is recognized that BPs are not approved for the treatment of pediatric GiOP, and BP use is considered off-label in this setting. However, BP therapy is often recommended in children with clinically significant fracture history and ongoing risk factors, eg, systemic GC therapy (Ward et al, 2016). Therefore, the decision to use BP in these subjects will be left to the medical judgment of the investigator, and BP use would not be proscribed by the protocol in this situation.

2.4 Rationale

A non-clinical study in skeletally mature (8-month-old) human RANKL knock-in mice challenged with subcutaneous (SC) slow-release prednisolone pellets showed that denosumab treatment fully prevented the reductions in BMD and strength of lumbar vertebrae observed in vehicle-treated mice and was associated with significant reductions in bone resorption parameters. These findings indicate that denosumab can prevent loss of bone mass and strength secondary to GC therapy.

Clinical data currently available with denosumab that are relevant to GiOP include a subset of adult subjects with rheumatoid arthritis who were receiving GCs in the denosumab phase 2 Study 20040144, in which administration of denosumab 60 mg or 180 mg every 6 months (Q6M) led to increased BMD at lumbar spine and total hip (Dore et al, 2010). In addition, denosumab has been investigated in a clinical trial of adults with GiOP (Study 20101217 [Saag et al, 2018]).

This study is part of a Pediatric Investigation Plan for denosumab (Prolia) that was agreed upon with the European Medicines Agency. The purpose of this study is to evaluate the efficacy, safety, and PK of denosumab (1 mg/kg BW, up to a maximum of 60 mg, administered SC Q6M) in pediatric subjects with GiOP. The selection of the 1 mg/kg BW Q6M dose is based on the following considerations:

- The pharmacodynamic effects of denosumab were similar in neonatal and adolescent animal models
- The pharmacodynamic effect of denosumab on inhibition of bone resorption in clinical studies in adult subjects is maintained over the 6-month dosing interval
- The PK profile of monoclonal antibodies, such as cetuximab (Erbitux prescribing information, 2012), bevacizumab (Glade Bender et al, 2008; Gordon et al, 2001), and infliximab (Fasanmade et al, 2011), is similar in pediatric and adult populations
- The PK of denosumab is not affected by age across all populations studied, with an age range of 28 to 87 years (Sutjandra et al, 2011)

Based on these data, the PK and pharmacodynamics of denosumab are expected to be similar between the adult and pediatric populations, thus supporting selection of the 1 mg/kg BW Q6M dose. This dose is equivalent to the approved 60 mg adult dose for denosumab (assuming a 60 kg subject), which was also the dose investigated in the adult GiOP trial (Study 20101217 [Saag et al, 2018]). In addition, denosumab PK will be assessed throughout the study to further characterize exposure/response relationship in the pediatric GiOP population.

A feasibility analysis of the study sites has shown difficulties in identifying appropriate per protocol patients that meet the diagnostic criteria of GiOP (International Society for Clinical Densitometry [ISCD], 2019; Bishop et al, 2014) with a specific inclusion criterion for evidence of at least 1 vertebral compression fracture of Genant grade 1 or higher, OR presence of both clinically significant fracture history and lumbar spine BMD Z-score ≤ -2.0. This inclusion criteria is the primary reason for a screen failure rate of ~70% to 75% in this study.

In addition, trends in pediatric GiOP over time using real-world data from 3 different databases: 1) United States (US) MarketScan, 2) United Kingdom (UK) Clinical Practice Research Datalink (CPRD), and 3) Germany Electronic Medical Records (EMR) supported the findings in the feasibility analysis.

Based on agreement with regulatory agencies, sample size for this study will be reduced to 24 subjects including at least 16 evaluable subjects for the primary analysis.

This study will be conducted per local regulatory and ethics committee/investigation review board requirements/guidelines, and data from this study may be used to seek modification of regional denosumab prescribing information.

2.5 Clinical Hypotheses

The hypothesis of this study is that the change from baseline in lumbar spine BMD Z-score following 12 months of denosumab treatment in children 5 to 17 years of age with GiOP will be greater than placebo.

3. EXPERIMENTAL PLAN

3.1 Study Design

The overall study design is described by a study schema at the end of the protocol synopsis section.

This is a phase 3 multicenter, randomized, double blind, placebo-controlled, parallel group study in pediatric subjects, age 5 to 17 years, with GiOP. Twenty-four subjects will be enrolled with at least 16 evaluable subjects for the primary analysis. Subjects will be randomized in a 2:1 (active:placebo) allocation ratio to receive either denosumab 1 mg/kg BW (up to a maximum of 60 mg) SC Q6M or matching placebo SC Q6M. Up to 15 subjects at selected sites will be given the opportunity to participate in a PK [redacted] substudy. The study is comprised of 2 periods, a 24-month treatment period (including a 12-month placebo-controlled period and a 12-month open-label period) and a 12-month observation period. At the end of the first 12 months of the placebo-controlled treatment

period, all subjects will receive open-label denosumab Q6M for 12 months. Upon completion of the 24-month treatment period, the 12-month observation period will begin. Daily supplements of calcium and vitamin D will be given to all subjects during the 24-month treatment period. Daily supplements of calcium and vitamin D may also be given to subjects during the 12-month observation period, if deemed medically warranted by the investigator. The planned length of participation in the study for an individual subject is approximately 3 years, which includes screening (up to 35 days), treatment phase (24 months), and off-treatment observation period (12 months). The anticipated dropout rate is approximately 10% in the first year.

Treatment Period

The treatment period will last for 24 months, including 12-month double-blind and 12-month open-label treatment. During the first 12 months of the placebo-controlled treatment period, subjects will receive either denosumab 1 mg/kg BW (up to a maximum of 60 mg) SC Q6M or matching placebo SC Q6M. At the end of the first 12 months of the treatment period, all subjects will receive open-label denosumab Q6M for 12 months. The last dose of study medication will be administered at month 18.

Observation Period

The observation period will start immediately after the 24-month treatment period and last 12 months, during which study subjects will receive no investigational product. Study subjects are to be followed up during the 12-month observation period according to the following guidelines:

- Subjects who are currently on systemic GC for the treatment of the underlying non-malignant condition(s) at the month 24 visit should discontinue investigational product and transition to another osteoporosis treatment per local standard of care, according to the medical judgment of the investigator, for an additional 12 months or until systemic GC treatment is discontinued (see Section 2.3.6)
- Subjects who are no longer on systemic GC for the treatment of the underlying non-malignant condition(s) at the month 24 visit should discontinue investigational product and be followed up for an additional 12 months off treatment; however, subjects who, during the 12-month observation period, resume systemic GC therapy, experience a worsening of their osteoporosis, or require osteoporosis therapy based on the medical judgment of the investigator may resume osteoporosis treatment per local standard of care at the discretion of the investigator

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

The study will be conducted in approximately 40 sites in North America, Europe, South America, Asia, and The Middle East.

Sites that do not enroll subjects within 6 months of site initiation may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

Twenty-four subjects will be enrolled with at least 16 evaluable subjects for the primary analysis. Subjects will be randomized in a 2:1 (active:placebo) allocation ratio. Up to 15 enrolled subjects (at selected sites) will be given the opportunity to participate in a PK [redacted] substudy.

Refer to Section 10.2 for additional information regarding the determination of the sample size.

3.4 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The planned length of participation in the study for an individual subject is approximately 3 years, which includes screening (up to 42 days), treatment phase (24 months), and off-treatment observation period (12 months). The anticipated dropout rate is approximately 10% in the first year. After signing the informed consent form (ICF), subjects should be randomized within 35 days.

3.5.2 End of Study

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when the last subject has completed the assessments for month 12.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study date is defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.

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 (eg, date of screening). This log may be completed and updated via an Interactive Voice Response (IVR)/Interactive Web Response (IWR) system.

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1). In addition to written informed consent from a legally acceptable representative, the assent of the child also must be obtained, as appropriate if requested by the institutional review board/independent ethics committee (IRB/IEC).

If the subject reaches the age of consent during the duration of the study, once the subject reaches the age of maturation (usually 18 years), the previously acquired parental consent is no longer applicable and the participant's consent must be obtained. Per International Conference for Harmonisation (ICH) E11 (R1), during clinical studies there is a requirement for obtaining adequate informed consent for continued participation from pediatric participants once a child reaches the age of legal consent. Local regulations related to confidentiality and privacy of pediatric participants must be followed.

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

101 Subject's legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated

102 Male or female subjects, age 5 to 17 years, inclusive, at the time of informed consent

Clinical diagnosis of GiOP as defined by the following (and consistent with the International Society for Clinical Densitometry definition of osteoporosis in children and adolescents [Bishop et al, 2014]):

103 A confirmed diagnosis of non-malignant condition(s) requiring treatment with systemic GC (including, but not limited to, chronic rheumatologic, gastrointestinal, neurologic, respiratory, and/or nephrological conditions)

- Subjects who are on systemic GC only as replacement therapy for adrenal insufficiency are not eligible for the study

104 Treatment with systemic GC (intravenous or oral) of any duration for the underlying non-malignant condition(s) within the 12 months prior to screening

- Prepubertal children should be expected to require significant GC use during the study, per investigator opinion

105 Evidence of at least 1 vertebral compression fracture of Genant grade 1 or higher, as assessed by the central imaging vendor on lateral spine X-rays performed at screening or within 2 months prior to screening; or, in the absence of vertebral compression fractures, presence of both clinically significant fracture history (ie, $\geq$ 2 long-bone fractures by age 10 years or $\geq$ 3 long-bone fractures at any age up to 17 years) and lumbar spine BMD Z-score $\leq$ -2.0, as assessed by the central imaging vendor

4.1.2 Exclusion Criteria

201 Current hyperthyroidism (unless well controlled on stable antithyroid therapy)

202 Current clinical hypothyroidism (unless well controlled on stable thyroid replacement therapy)

203 History of hyperparathyroidism

204 Current hypoparathyroidism

205 Any causes of primary or secondary osteoporosis (other than GC use), or previous exposure to non-GC medications, which the investigator considers to have been a major factor contributing to the patient's fracture(s)

206 Current adrenal insufficiency as the sole indication for GC therapy

207 Duchenne muscular dystrophy with symptomatic cardiac abnormality

208 Current malabsorption (in children with serum albumin $<$ lower limit of normal [LLN], malabsorption should be clinically ruled out by the investigator to confirm eligibility)

209 Known intolerance to calcium or vitamin D supplements

Active infection or history of infections, defined as follows:

210 Any active infection for which systemic anti-infectives were used within 4 weeks prior to screening

211 Serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to screening

212 Recurrent or chronic infections or other active infection that, in the opinion of the investigator, might compromise the safety of the subject

213 History of malignancy

214 History of any solid organ or bone marrow transplant

215 Evidence of untreated oral cavities or oral infections

216 Recent or planned invasive dental procedure

217 Surgical tooth extraction which has not healed by screening

218 Currently unhealed fracture or osteotomy, as defined by orthopedic opinion

219 Osteotomy within 5 months prior to screening

220 Spinal fusion surgery within 5 months prior to screening or not yet healed (per orthopedic surgeon)

221 Rodding surgery within 5 months prior to screening or not yet healed (per orthopedic surgeon)

222 Anticipated major skeletal surgery (eg, rodding surgery, spinal surgery) within the next 12 months from day 1

223 Planned orthopedic surgery that, in the opinion of the investigator, would require missing any dose of investigational product in year 1 or 2 or more doses thereafter

224 History of rare hereditary problems of fructose intolerance

225 History of long QT syndrome

226 History of alcohol or drug abuse

227 History or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion

228 Serum albumin-corrected calcium < LLN or > 10% above upper limit of normal (ULN) at screening

229 Serum vitamin D < 20 ng/mL at screening (rescreening for vitamin D level < 20 ng/mL will be allowed, after adequate supplementation)

230 Serum phosphorus < LLN at screening

231 Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 1.5 x ULN (or > 5 x ULN in subjects with dystrophinopathies) at screening

In subjects with dystrophinopathies, AST or ALT elevation > 5 x ULN may not be exclusionary if

i. It is associated with serum creatine phosphokinase (CPK) elevation

AND

ii. Serum total bilirubin, alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), and prothrombin time/international normalized ratio (PT/INR) are < ULN, and serum albumin is > LLN

AND

iii. There are no symptoms or signs of hepatic inflammation, such as nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, with no other immediately apparent possible cause (eg, gastroenteritis or constipation)

232 Serum total bilirubin > 1.5 x ULN at screening (subjects with Gilbert syndrome are eligible)

233 Positive blood screen for human immunodeficiency virus (HIV)-1 or -2 antibody

234 Positive blood screen for hepatitis B surface antigen or hepatitis C antibody

235 Estimated glomerular filtration rate $<$ 60 mL/min/1.73 m^2 at screening (calculated by the bedside Schwartz equation)

236 Less than 2 evaluable vertebrae by DXA evaluation in the region of interest L1-L4, as confirmed by the central imaging laboratory

Prior treatment for bone disease with any of the following at any time:

237 Denosumab

238 Strontium

239 Fluoride

Recent BP treatment, according to the following guidelines:

240 Zoledronic acid (ZA) within 6 months prior to screening (subjects are eligible if 6 months will have elapsed, since the previous ZA dose, by the time of first dose of investigational product)

241 Oral BP or intravenous BP (other than ZA), if the first dose of investigational product would be before their next scheduled BP dose (subjects are eligible if at least 1 BP dosing interval will have elapsed at time of the first dose of investigational product)

Administration of any of the following treatment within 3 months prior to screening:

242 Growth hormone (unless on stable dose for at least 3 months prior to screening)

243 Calcitonin

244 Cathepsin K inhibitor

245 Other bone active drugs including anti-convulsants (except gabapentin and benzodiazepines) and heparin

246 Chronic systemic ketoconazole, androgens (except subjects who have received testosterone therapy for physiologic replacement in the setting of documented hormonal deficiency), cinacalcet, aluminum, lithium, protease inhibitors, gonadotropin releasing hormone agonists

Initiation of any of the following biologic agents within 4 weeks prior to screening:

247 Anti-alpha 4 integrin antibody (eg, natalizumab)

248 Anti-CD4/CD8 T-cells (eg, alefacept)

249 Anti-IL-12/IL-23 (eg, ustekinumab)

250 CTLA4 inhibitor (eg, abatacept)

251 IL1 receptor antagonist (eg, anakinra)

252 IL6 inhibitor (eg, tocilizumab)

253 Monoclonal antibody to CD20 (eg, rituximab)

254 Tumor necrosis factor antagonist (eg, adalimumab, certolizumab, golimumab, etanercept, infliximab)

255 Current treatment with $>$ 1 biologic agent for underlying inflammatory disease

256 Currently pregnant or planning a pregnancy during the study and for an additional 5 months after the last dose of investigational product

257 Currently breastfeeding or planning on breastfeeding during the study and for an additional 5 months after the last dose of investigational product

258 For sexually active girls: refusal to use highly effective methods of contraception and to continue this practice for 5 months after the last injection of investigational product

259 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.

260 Subject's parent or legal representative has any kind of disorder that, in the opinion of the investigator, may compromise the ability to give written parental permission for informed consent

261 Currently receiving treatment in another investigational device or drug study, or $<$ 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written IRB/IEC approval of the protocol, ICF, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All legally acceptable representatives must personally sign and date the ICF, and subjects should sign the subject assent form as applicable by local law before commencement of study specific activities/procedures.

A subject is considered enrolled when the investigator confirms that the subject has met all eligibility criteria. The investigator is to document this decision and date in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined as when the informed consent and subject assent forms are duly signed) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by an IVRS/IWRS. 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 after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

5.1 Screening

After signing the informed consent, and assent if applicable, subjects will be screened in order to assess their eligibility for study participation. The screening window is up to 35 days. If a subject has not met all eligibility criteria during or by the end of the screening window, the subject will be registered as a screen failure. Subjects who screen fail may be eligible to rescreen per Section 7.2.2.

5.2 Randomization

Subjects will be randomized in a 2:1 allocation ratio to receive either denosumab or placebo respectively, in a double-blind manner. The randomization will be performed by IVR/IWR system. The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

5.3 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Amgen Clinical Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

6. TREATMENT PROCEDURES

Subjects will be randomized to receive denosumab or placebo every 6 months in a 2:1 allocation ratio for the first 12 months. At the end of the initial 12-month period, all subjects will receive open-label denosumab Q6M for 12 months. Denosumab administered at a dose of 1 mg/kg BW (up to a maximum of 60 mg) and matching placebo are considered to be IPs in this study. A manual containing detailed information regarding the storage, preparation, and administration of investigational product are provided separately in the Investigational Product Instruction Manual (IPIM).

All subjects will receive a SC injection of investigational product Q6M for the first 12 months. At the end of the initial 12-month placebo-controlled period, all subjects will receive open-label denosumab Q6M for 12 months (last injection to be administered at month 18). All SC injections must be administered by authorized site personnel. The injection should not be administered in the same arm from which blood is drawn. Investigational product should be administered only after all other study visit procedures have been completed. If a subject misses a scheduled dose of investigational product during a study visit, then he/she should return to the clinic to receive the missed dose

within the visit window allowed for that particular visit (see Section 7). The clinical monitor should be contacted for specific instructions if a subject cannot receive his/her dose within the allowed visit window.

The total volume of investigational product, start date/time, and box number of investigational product are to be recorded on each subject's CRF.

Overdose with this product has not been reported. The highest dose tested in clinical trials is 210 mg SC Q6M. 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.

6.1 Classification of Products

The Amgen investigational product and/or placebo (except if required by local regulation) used in this study include: denosumab, placebo.

The non-Amgen non-investigational products used in this study include: calcium, vitamin D.

The IPIM, a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of denosumab.

6.2 Amgen Investigational Product

Denosumab and placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Denosumab will be presented as a 70 mg/mL solution containing 1.7 mL in a 3 mL vial. Placebo will be presented as a solution identical in appearance to denosumab, without the active ingredient.

6.2.1 Dosage, Administration, and Schedule

All subjects will receive a SC injection of investigational product Q6M for 24 months (last injection to be administered at month 18). Each subject will receive a total of 2 double-blind, randomized doses (either denosumab or placebo) over the first 12 months (given at the day 1 and month 6 visits) and a total of 2 open-label denosumab doses over the following 12 months (given at the month 12 and month 18 visits). All SC injections must be administered by authorized site personnel. The injection should not be administered in the same arm from which blood is drawn. Investigational product should be administered only after all other study visit procedures have been completed.

The total volume of investigational product, start date/time, and box number of investigational product are to be recorded on each subject's CRF.

Overdose with this product has not been reported. The highest dose tested in clinical trials is 210 mg SC Q6M. 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.

6.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

There are no dose adjustments for the Amgen investigational product. If a subject misses a scheduled dose of denosumab during a study visit, then he/she should return to the clinic to receive the missed dose within the visit window allowed for that particular visit (see Section 7). The clinical monitor should be contacted for specific instructions if a subject cannot receive his/her dose within the allowed visit window.

Administration of Amgen investigational product will be stopped for subjects in the following situations:

1. Subject request
2. Safety concern due to:
    a. Ineligibility determined
    b. Protocol deviation
    c. Noncompliance
    d. Requirement for alternative therapy
    e. Adverse event (but not limited to):
        - Severe or symptomatic hypocalcemia
            - Subjects who are removed from treatment as a result of severe or symptomatic hypocalcemia should receive treatment according to local standard of care, at the discretion of the treating physician and should be closely followed up until resolution of the adverse event
        - Osteonecrosis of the jaw
        - Serious opportunistic infection
3. Decision by sponsor (other than subject request or safety concern)
4. Death
5. Lost to follow-up
6. Pregnancy

7. Other protocol-specified criteria:
    a. ≥ 4 new fractures in 6 months
    b. > 2 new long-bone fractures in 6 months
    c. Decline in lumbar spine BMD Z-score by 0.5 units or more in 6 months
        - Subjects who are removed from treatment as a result of criterion a, b, or c (above) should be followed up and treated, if applicable, according to local standard of care, at the discretion of the treating physician
    d. Changes in growth plate morphology, as observed in the 6-month monitoring, considered by the investigator to be unexpected and having an adverse clinical impact for the subject
    e. Disease flare requiring treatment not allowed in the protocol
    f. Dental abnormalities requiring invasive dental procedures
    g. Serious infection, if the subject is receiving a biologic agent for the treatment of underlying inflammatory disease
        - Serious infection is defined as a serious adverse event of infection that is complicated by multiple organ involvement or sepsis
            – Sepsis is defined by the presence of infection and a severe systemic inflammatory response

If a subject discontinues Amgen investigational product, the investigator is to discuss with the subject the appropriate processes for discontinuation and the options for continuation of the Schedule of Assessments and collection of data, including endpoints and adverse events, as applicable. The investigator must document the change to the Schedule of Assessments and the level of follow up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

6.3 Non-Amgen Non-investigational Product(s)

Non-Amgen non-investigational product(s) including calcium and vitamin D supplements will also be used in this study. These therapies are commercially available and are not provided by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies and will be reimbursed.

The dose, start date, stop date, and frequency for calcium and vitamin D are to be recorded on each subject's CRF. At screening, the investigator or designee will instruct subjects on daily calcium and vitamin D supplementation.

Additional details regarding the product(s) are provided in the IPIM.

The below clarifies use of the activated form of 1-25 OH vitamin D (Calcitriol):

Calcitriol is allowed for use when in cases where medically indicated and no other exclusionary medical history is present. Recommended doses in the pediatric population are:

- Children under 1 year: 0.04-0.08 mcg/kg orally once/day.
- Children 1-5 years: 0.25-0.75 mcg orally once/day.
- Children over 6 years: 0.5-2 mcg orally once/day.

Calcitriol may not be used as an adjuvant treatment for osteoporosis and rationale for use must be documented in the CRF.

6.3.1 Non-Amgen Non-investigational Product: Calcium

All subjects are required to take daily supplements of 30 to 50 mg/kg BW and not to exceed 1000 mg elemental calcium during the 24-month treatment phase of the study.

6.3.2 Non-Amgen Non-investigational Product: Vitamin D

All subjects are required to take daily supplements of at least 800 IU vitamin D during the 24-month treatment phase of the study.

6.3.3 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

If a subject becomes hypercalcemic over the course of the study, the calcium and/or vitamin D supplementation may be discontinued until the serum calcium concentration has returned to the normal range. If a subject becomes hypocalcemic over the course of the study, the calcium and/or vitamin D supplementation may be increased, per medical judgment of the investigator.

In instances where a subject is experiencing tolerability issues with daily elemental calcium, the subject should be instructed to try different calcium salt formulations. If this strategy fails, the investigator may document that only a lower calcium supplementation dose is tolerated by the subject or that dietary supplementation is required and this will be allowed. Tolerability issues for vitamin D should be managed using the same approach as outlined for calcium above.

The reason for dose change of calcium and/or vitamin D supplementation is to be recorded on each subject's CRF.

6.4 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, ALP, AST, ALT, TBL) and/or INR and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.4.1 Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR, and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
- Right-sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic Fatty Liver Disease including Steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

Amgen investigational product and other protocol-required therapies, as appropriate, should be withheld pending investigation into alternative causes of Drug Induced Liver Injury (DILI). If investigational product(s) is/are withheld, the subject is to be followed for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline.

Permanent discontinuation of investigational product is recommended if all of the following apply:

- TBL > 2 x ULN or INR > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT elevation
< ULN	> 3 x ULN

- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent (eg, hepatobiliary tract disease, viral hepatitis, right-sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia, etc)

Conditional withholding of investigational medicinal product or other protocol-required therapies is recommended if all of the following apply:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	> 8 x ULN at any time
Any	> 5 x ULN but < 8 x ULN for ≥ 2 weeks
Any	> 5 x ULN but < 8 x ULN and unable to adhere to enhanced monitoring schedule
Any	> 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice).

- OR: TBL > 3 x ULN at any time
- OR: ALP > 8 x ULN at any time

In subjects with dystrophinopathies, given the well-known occurrence of serum transaminase elevation of muscular origin (McMillan et al, 2011), conditional withholding of investigational medicinal product or other protocol-required therapies is recommended if the above elevations in AST or ALT are:

- Not accompanied by corresponding CPK elevations

  OR

- Accompanied by concomitant TBL, ALP, GGT, or PT/INR elevation and/or symptoms or signs of hepatic inflammation, such as nausea, vomiting, right upper quadrant pain or tenderness, jaundice, or fever, with no other immediately apparent possible cause (eg, gastroenteritis or constipation)

6.4.2 Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, the subject's legally acceptable representative, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then denosumab should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.4.1) should never be rechallenged.

6.5 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 6.7.

Concomitant therapies are to be collected from informed consent through the end of study. Collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

6.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.7 Excluded Treatments and/or Procedures During Study Period

All medications listed in the exclusion criteria, those shown in Table 1 below, or any other medication that is known or suspected to have activity on bone metabolism (except for GCs, calcium, and vitamin D) will not be allowed during the study.

Table 1. List of Proscribed Therapy

• Aluminum • Anabolic steroids • Androgens[a] • Anticonvulsants (gabapentin and benzodiazepines are allowed) • Any investigational agents for bone loss other than investigational product • Aromatase inhibitors • > 1 biologic agent for the treatment of underlying inflammatory disease • Bisphosphonates (a cumulative dose of ≥ 30 days)[b] • Calcitonin	• Calcium chelators • Chemotherapeutics (except for methotrexate, azathioprine, 6-mercaptopurine, thioguanine, leflunomide, and cyclosporine) • Chronic heparin use (> 7 days) • Cinacalcet • Citrated products • Fluoride • Gonadotropin-releasing hormone agonists • Growth hormone (unless stable for at least 3 months prior to screening) • Lithium	• Parathyroid hormone (or a derivative) • Progestins, when used as monotherapy • Protease inhibitors • Strontium • Tibolone

Footnote is defined on next page
[a] Except subjects who are receiving testosterone therapy for physiologic replacement in the setting of documented hormonal deficiency
[b] Bisphosphonates are not proscribed medications if prescribed per local standard of care, according to the medical judgement of the investigator, after investigational product discontinuation during the, 1) 24-month treatment period (see Section 6.2.2) or, 2) 12-month observation period (see Sections 2.3.6 and 3.1)

6.8 Contraceptive Requirements

Female of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females are considered of childbearing potential if they have had menarche or are Tanner stage 2 or higher. Female subjects who have had menarche or are Tanner stage 2 or higher will need to have pregnancy testing.

Females in the following categories are not considered of child bearing potential:

1. Premenopausal female with 1 of the following:
   a. Documented hysterectomy
   b. Documented bilateral salpingectomy
   c. Documented bilateral oophorectomy

Note: Site personnel documentation from the following sources is acceptable: 1) review of subject medical records, 2) subject medical examination, or 3) subject medical history interview.

2. Premenarchal female (unless of Tanner Stage 2 or higher)
3. Postmenopausal female

a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient.

b. Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

6.8.1 Female Subjects

Female subjects of childbearing potential must agree to use 1 highly effective method of contraception (as described in the table below) during treatment and for an additional 5 months after the last dose of protocol-required therapies.

Highly Effective Contraceptive Methods for Female Subjects *Failure rate of < 1% per year when used consistently and correctly.*
• Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
• Intrauterine device
• Intrauterine hormonal-releasing system
• Bilateral tubal ligation/occlusion
• Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
• Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)

If a female subject is suspected of being pregnant, the protocol-required therapies must be stopped immediately and may not be resumed until absence of pregnancy has been medically confirmed.

6.8.2 Male Subjects

Male subjects are not required to use birth control during exposure to denosumab.

6.8.3 Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include: periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to fetus if they become pregnant during treatment and for 5 months after the last dose of investigational product.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Screening assessments and study procedures required for each visit are outlined in this section and the Schedule of Assessments (Table 2). The informed consent, and assent if applicable, must be obtained prior to performing any screening or study procedures. All subjects randomized to denosumab will have samples assayed for binding and, if positive, neutralizing antibodies.

Table 2. Schedule of Assessments

	Screening Period	Treatment Period								Observation Period	
		Study Day			Study Month						
Procedures	Study Day -35[a] to -1	1	10	30	3	6	12	18	24	30	36/ET[b]
			± 3-day window		± 7-day window						
Informed consent and assent form (if applicable)	X										
Medical and medication history	X										
Physical examination	X	X			X	X	X	X	X	X	X
Tanner stage	X					X[c]	X	X[c]	X	X[c]	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Height	X	X				X	X	X	X	X	X
Weight	X	X				X	X	X	X	X	X
Arm span	X						X		X		X
DXA (lumbar spine)[d]	X[e]					X	X	X	X		X
DXA (proximal femur)[d,f]		X[e]				X	X	X	X		X
X-ray (lateral thoracic, lumbar spine)[d]	X[g]						X		X		X
X-ray – AP knees[d,h,i]		X				X	X	X	X	X	X
Dental X-ray (cephalogram and panoramic radiograph)[d]		X									X
Oral visual inspection							X		X		
Dental X-ray (molars)[d,j]							X		X		
Hematology	X	X			X	X	X	X	X	X	X
Serum chemistry	X	X	X	X[k]	X	X	X	X	X	X	X
Serology for HIV, hepatitis B, and hepatitis C	X										
Serum CPK, GGT, and PT/INR[l,m]	X										

Footnote defined on last page of the table

Table 2. Schedule of Assessments

	Screening Period	Treatment Period								Observation Period	
		Study Day			Study Month						
Procedures	Study Day -35[a] to -1	1	10	30	3	6	12	18	24	30	36/ET[b]
			± 3-day window		± 7-day window						
25(OH) vitamin D level	X										
Pregnancy test (urine dipstick method)[n]	X	X				X	X	X	X	X	X
SC injection of investigational product (denosumab/placebo)[o]		X				X	X	X			
Dispensation of calcium and vitamin D		X				X	X	X			
Antidenosumab antibody assay		X		X	X	X	X		X		
Concomitant medications		X	X	X	X	X	X	X	X	X	X
PK (serum denosumab)		X	X	X[p]	X[p]	X	X	X			
[redacted]											
Adverse events		←	—	—	—	—	—	—	—	—	→
Serious adverse events[q]	←	—	—	—	—	—	—	—	—	—	→
Product complaints		←	—	—	—	—	—	—	→		
Clinical fracture recording		X	X	X	X	X	X	X	X	X	X
Administration of:											
CHQ-PF-50		X					X		X		X
CHAQ Disability Score		X					X		X		X
Wong-Baker Faces Pain Scale		X					X		X		X

Footnote defined on next page

ALT = Alanine aminotransferase; AP = Anteroposterior; AST = Aspartate aminotransferase; [redacted] CPK = Creatine phosphokinase, DILI = Drug-induced liver injury; DXA = Dual-energy X-ray absorptiometry, CHAQ = Childhood Health Assessment Questionnaire, CHQ-PF-50 = Childhood Health Questionnaire-Parent Form-50, ET = Early termination; GGT = gamma-glutamyltransferase, HIV = Human immunodeficiency virus; INR = International normalized ratio; PK = Pharmacokinetic, PT = Prothrombin time; Q6M = every 6 months; SC = Subcutaneous, [redacted] ULN = Upper limit of normal; WBFPRS = Wong-Baker Faces Pain Scale.

[a] Day -42 for rescreening only
[b] If the subject discontinues the study prior to the month 36 visit, a safety follow-up visit will occur within 30 days following the last protocol-required therapy
[c] Tanner stage to be conducted at months 6, 18, and 30 only in female subjects to determine the need to perform a pregnancy urine dipstick test at these visits
[d] All images/reports (as applicable) to be sent to the central imaging vendor
[e] To be performed in duplicate at this visit only
[f] May be performed at screening to facilitate subject scheduling
[g] For subjects who have qualified based on long-bone fracture criteria, the baseline lateral spine radiograph may be obtained on day 1 instead
[h] To be performed only in children with open growth plates who do not have bilateral hardware
[i] Only the knee with the highest metaphyseal index Z-score on the day 1 bilateral knee X-ray should be X-rayed post day 1
[j] To be performed based on oral visual inspection
[k] On study day 30, blood collection may be performed by a qualified individual at the subject's home, in lieu of a site visit, except for subjects participating in the PK/[redacted]substudy. In addition, when blood collection is performed at the subject's home, the investigator must ensure that concomitant medications and adverse events, if any, are appropriately recorded.
[l] To be performed in subjects with dystrophinopathies only
[m] PT/INR to be performed at screening only in subjects with dystrophinopathies who have AST or ALT > 5 x ULN and at subsequent visits in any subjects for the purpose of DILI ascertainment, as applicable (see Section 6.4)
[n] To be performed in female subjects who have had menarche or those who are Tanner stage 2 or higher
[o] At month 12, all subjects will receive open-label denosumab Q6M for 12 months
[redacted]
[q] After the protocol required reporting period or after end of study, serious adverse events will be reported to Amgen. Please refer to Section 9.2.1.5 for additional details.

Refer to the applicable supplemental manuals (eg, laboratory, imaging) for detailed collection and handling procedures.

7.2 General Study Procedures

All on-study visits and dosing should be scheduled from day 1. It is important to perform study assessments and obtain samples at the time points outlined in the Schedule of Assessments (Table 2).

When it is not possible to perform the study visit at the specified time point, the visit may be performed within the visit window noted in the Schedule of Assessments (Table 2). If a study visit is missed, subsequent visits should resume on the original visit schedule. Missed assessments at prior visits should not be duplicated at subsequent visits.

With the exception of screening or rescreening visits, all study procedures for a visit must be completed on the same day.

It is the responsibility of the investigator to ensure that all procedures are performed according to the protocol.

Details regarding each type of procedure are provided in Section 7.3.

7.2.1 Screening

Screening and day 1 visit cannot occur on the same day. The day 1 visit needs to occur within 35 days of the screening date (unless the subject is rescreened).

The following procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 2):

- Confirmation that the ICF and Assent form (if applicable) have been signed
- Demographic data including sex, date of birth, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally demographic data will be used to study the impact biomarker variability and PK of the protocol-required therapies.
- Registration in IVR/IWR system
- Medical and medication history
- Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history)
- Tanner stage
- Vital signs
- Height
- Weight
- Arm span

- DXA (lumbar spine) (To be performed in duplicate at this visit only. All images/reports [as applicable] to be sent to the central imaging vendor.)
- X-ray (lateral thoracic spine) (For subjects who have qualified based on long-bone fracture criteria, the baseline lateral spine radiograph may be obtained on day 1 instead. All images/reports [as applicable] to be sent to the central imaging vendor)
- Hematology
- Serum chemistry
- Serology for HIV, hepatitis B, and hepatitis C
- Serum CPK, GGT, and PT/INR (to be performed at screening only in subjects with dystrophinopathies who have AST or ALT $>$ 5 x ULN)
- 25(OH) vitamin D level
- Pregnancy test (urine dipstick method) (to be performed in female subjects who have had menarche or those who are Tanner stage 2 or higher)
- Serious adverse events/fractures

7.2.2 Rescreening

Rescreening will be allowed as follows. A new ICF must be signed unless it has been $<$ 30 days since the previous ICF signature was obtained. Subjects may be rescreened only once for each of the 2 conditions below (rescreening for serum 25 **[**OH**]** vitamin D and/or full rescreening for other reasons of screen failure). Sites will be notified, near the end of enrollment for the study, when subjects can no longer be rescreened. After this notification, subjects who do not qualify based on their initial tests will be screen failed.

Rescreening for Serum 25(OH) Vitamin D

For subjects with an initial screening serum 25(OH) vitamin D level $<$ 20 ng/mL, rescreening will be performed as follows:

- Enter the subject as a screen failure into the IVRS/IWRS and enter him/her as a rescreen. Subjects not entered into IVRS/IWRS as a rescreen will not be eligible to participate in the study.
- A new 42-day screening window will commence at this time.
- The subject must be repleted for vitamin D, as confirmed by a serum vitamin D level $\geq$ 20 ng/mL obtained by the central laboratory prior to the day 1 visit, to meet subject eligibility requirements.

Full Rescreening

Full rescreening will be allowed for any subject who has previously failed screening if, in the opinion of the investigator, the reason for the initial screen failure has been resolved or is no longer applicable.

Full rescreening will be performed according to the following procedure:

- Reassess only the procedure(s) that did not meet screening standards initially in subjects who are rescreened within 84 days of screen failure
- Reassess all the screening procedures, except for radiologic procedures and serology for HIV, hepatitis B virus, and hepatitis C virus, in subjects who are rescreened $>$ 84 days, but $<$ 6 months, after screen failure
- Reassess all the screening procedures in subjects who are rescreened $\geq$ 6 months after screen failure
- Subjects must be enrolled within the new 42-day rescreening window
- A new ICF must be signed unless it has been $<$ 30 days since the previous ICF signature was obtained

7.2.3 Day 1

At the completion of the screening period, when the subject has met all eligibility criteria, sites will need to complete the randomization call in the IVR/IWR system. The initial dose of investigational product is to be administered within 3 days of confirming randomization. The date that the initial procedures are performed postrandomization will be considered day 1. All subsequent study visits will be scheduled based on the day 1 date.

- Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history)
- Vital signs
- Height
- Weight
- DXA (proximal femur) (To be performed in duplicate at this visit only. All images/reports [as applicable] to be sent to the central imaging vendor.) (Note: this may be done at screening in order to facilitate subject scheduling)
- X-ray (anterioposterior [AP] knees) (To be performed only in children with open growth plates who do not have bilateral hardware. All images/reports [as applicable] to be sent to the central imaging vendor.)
- Dental X-ray (cephalogram and panoramic radiograph) (All images/reports [as applicable] to be sent to the central imaging vendor.)
- Hematology
- Serum chemistry
- Pregnancy test (urine dipstick method) (To be performed in female subjects who have had menarche or those who are Tanner stage 2 or higher.)
- Dispensation of calcium and vitamin D
- Antidenosumab antibody assay
- Concomitant medications

- PK (serum denosumab)
- [redacted]
- Adverse events
- Serious adverse events
- Product complaints
- Clinical fracture recording
- Administration of:
  - CHQ-PF-50
  - CHAQ Disability Score
  - WBFPRS
- SC injection of investigational product (denosumab/placebo)

7.2.4 Treatment Period

7.2.4.1 Study Days 10 and 30

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 2). These study visits will occur ± 3 days. The following procedures and assessments will be completed at the times designated in the Schedule of Assessment (Table 2) and recorded on the CRF:

- Vital signs
- Serum chemistry (On study day 30, blood collection may be performed by a qualified individual at the subject's home, in lieu of a site visit, except for subjects participating in the PK/[redacted] substudy. In addition, when blood collection is performed at the subject's home, the investigator must ensure that concomitant medications and adverse events, if any, are appropriately recorded.)
- Concomitant medications
- PK (serum denosumab) (Serum denosumab concentrations will be collected at day 30 only in a PK [redacted] substudy of up to 15 subjects [additional consent for the substudy must be obtained].)
- [redacted]
- Antidenosumab antibody assay (days 1 and 30 only)
- Adverse events
- Serious adverse events
- Product complaints
- Clinical fracture recording

7.2.4.2 Study Months 3, 6, 12, 18, and 24 (Month 24 is Also Considered the Start of the Observation Period)

These study visits will occur ± 7 days. The following procedures and assessments will be completed at the times designated in the Schedule of Assessment (Table 2) and recorded on the CRF:

- Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history).
- Tanner stage (months 12 and 24 in all subjects, and months 6 and 18 in female subjects only to determine the need to perform a pregnancy urine dipstick test)
- Vital signs
- Height (months 6, 12, 18, and 24 only)
- Weight (months 6, 12, 18, and 24 only)
- Arm Span (months 12 and 24 only)
- DXA (lumbar spine) (All images/reports [as applicable] to be sent to the central imaging vendor) (months 6, 12, 18, and 24 only)
- DXA (proximal femur) (All images/reports [as applicable] to be sent to the central imaging vendor) (months 6, 12, 18, and 24 only)
- X-ray (lateral thoracic, lumbar spine) (All images/reports [as applicable] to be sent to the central imaging vendor) (months 12 and 24 only)
- X-ray (AP knees) (All images/reports [as applicable] to be sent to the central imaging vendor) (months 6, 12, 18, and 24 only)
- Oral visual inspection (months 12 and 24 only)
- Dental X-ray (molars) (To be performed based on oral visual inspection. All images/reports [as applicable] to be sent to the central imaging vendor) (months 12 and 24 only)
- Hematology
- Serum chemistry
- Pregnancy test (urine dipstick method) (To be performed in female subjects who have had menarche or those who are Tanner stage 2 or higher.) (months 6, 12, 18, and 24 only)
- Dispensation of calcium and vitamin D (months 6, 12, and 18 only)
- Antidenosumab antibody (months 3, 6, 12 and 24 only)
- Concomitant medications
- PK (serum denosumab) (To be collected at month 3 only in a PK [redacted] substudy of up to 15 subjects [additional consent for the substudy must be obtained].) (months 6, 12, and 18 only)

[redacted]

- Adverse events

- Serious adverse events
- Product complaints
- Clinical fracture recording
- Administration of:
  - CHQ-PF-50 (months 12 and 24 only)
  - CHAQ Disability Score (months 12 and 24 only)
  - WBFPRS (months 12 and 24 only)
- SC injection of investigational product (denosumab or placebo at month 6, denosumab at months 12 and 18)

7.2.5 Observation Period (Months 30 and 36)

These study visits will occur ± 7 days. The following procedures and assessments will be completed at the times designated in the Schedule of Assessment (Table 2) and recorded on the CRF:

- Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history)
- Tanner stage (month 36 in all subjects, and month 30 in female subjects only to determine the need to perform a pregnancy urine dipstick test)
- Vital signs
- Height (months 30 and 36 only)
- Weight
- Arm Span (month 36 only)
- DXA (lumbar spine) (All images/reports [as applicable] to be sent to the central imaging vendor) (month 36 only)
- DXA (proximal femur) (All images/reports [as applicable] to be sent to the central imaging vendor) (month 36 only)
- X-ray (lateral thoracic, lumbar spine) (All images/reports [as applicable] to be sent to the central imaging vendor) (month 36 only)
- X-ray (AP knees) (All images/reports [as applicable] to be sent to the central imaging vendor)
- Dental X-ray (cephalogram and panoramic radiograph) (month 36 only)
- Hematology
- Serum chemistry
- Pregnancy test (urine dipstick method) (To be performed in female subjects who have had menarche or those who are Tanner stage 2 or higher.)
- Concomitant medications
- [redacted]
- Adverse events
- Serious adverse events

- Clinical fracture recording
- Administration of:
  - CHQ-PF-50 (month 36 only)
  - CHAQ Disability Score (month 36 only)
  - WBFPRS (month 36 only)

7.3 Study Procedures

7.3.1 Data Collection

All laboratory values will be electronically transferred from the central laboratory to the Amgen database. The central imaging vendor will collect DXA and radiographic imaging and will electronically transfer the data to the Amgen database. All other data will be captured on the eCRF. Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

7.3.2 Medical History

The investigator or designee will complete a general medical/surgical history collected from 5 years prior to enrollment up to the time of enrollment and will be recorded on the eCRF. Medical history will include information on the subject's concurrent medical conditions. Fracture history and the condition for which GCs are/were administered must be recorded regardless of time frame.

7.3.3 Medication History

Medication history will be collected from 5 years prior to enrollment up to the time of enrollment and will be recorded on the eCRF.

7.3.4 Concomitant Medications

All concomitant medications, including over-the-counter products and vitamins administered while the subject is on the study, must be recorded on the eCRF. The generic name, indication, dose, frequency, and start and stop dates will be recorded.

7.3.5 Laboratory Assessments

Central Laboratory Chemistry	Central Laboratory Coagulation	Central Hematology	Serology	Other assessments
Sodium Potassium Chloride Bicarbonate Total protein Albumin 25(OH) vitamin D Calcium[a] Adjusted calcium[a] Magnesium Phosphorus[a] Glucose BUN Creatinine Total bilirubin Alk phos[a] AST (SGOT) ALT (SGPT) GGT[b] CPK[b]	PT/INR[c]	RBC Hemoglobin Platelets WBC Differential Eosinophils Basophils Lymphocytes Monocytes Neutrophils	HIV-1, -2 antibody HBsAg Hep C Ab	Serum denosumab[a] Anti denosumab antibody[a] [redacted]

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; [redacted] BUN = Blood urea nitrogen; CPK = Creatine phosphokinase; DILI = Drug-induced liver injury; GGT = Gamma-glutamyltransferase; HBsAg = Hepatitis B surface antigen; Hep C Ab = Hepatitis C antibody; HIV = Human immunodeficiency virus; INR = International normalized ratio; PT = Prothrombin time; RBC = Red blood cell; [redacted] ULN = Upper limit of normal; WBC = White blood cell.

[a] Results of post-day 1 assessments will be blinded to any study-related personnel (including the sites) except for serum calcium, albumin-adjusted calcium, phosphorus, or ALP in the event of a panic value

[b] To be performed only in subjects with dystrophinopathies at screening and at subsequent visits for the purpose of DILI ascertainment (if applicable)

[c] To be performed at screening only in subjects with dystrophinopathies who have AST or ALT > 5 x ULN and at subsequent visits in any subjects for the purpose of DILI ascertainment, as applicable (see Section 6.4)

7.3.6 Physical Examination

Physical examination will also include assessment of Tanner stage. A pelvic, breast, or rectal examination is not required unless a specific evaluation is warranted.

7.3.7 Physical Measurements

Physical measurements include height and weight. Height (in centimeters) and weight (in kilograms) should be measured without shoes. Height measurements will be performed in the standing position unless it is not possible to do so. Measurement of

standing height should be made using a wall-mounted stadiometer (calibrated within the previous 4 hours), and recorded to the nearest 10th of a centimeter (Food and Drug Administration Guidance for Industry, 2007). In instances where standing height cannot be measured, measurement of recumbent height will be allowed.

Body Mass Index should be calculated using the following formula:
BMI (kg/m^2) = weight (kg)/[height (cm)/100]^2.

7.3.8 Vital Signs

Vital signs will include temperature, respiration rate, blood pressure, and heart rate obtained in the sitting position after the subject has been sitting quietly for at least 5 minutes. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF.

7.3.9 Pregnancy Testing

Pregnancy tests will be performed from urine samples to be collected at screening, on day 1, and at months 6, 12, 18, 24, 30, and 36 in all female subjects who are at Tanner stage 2 (or higher) or have had menarche. A negative pregnancy test must be confirmed prior to administration of study medication at all scheduled visits (as applicable).

7.3.10 Dual-energy X-Ray Absorptiometry (DXA)

All subjects will undergo bone densitometry assessments of the lumbar spine and proximal femur performed by DXA at all applicable visits. DXA assessments of the lumbar spine and proximal femur are to be performed in duplicate only at screening and day 1, respectively. All DXA scans will be submitted to a central imaging vendor for analysis.

Only General Electric Lunar or Hologic bone densitometers will be allowed for this study. The same DXA machine must be used for all study procedures for a particular subject. The left side should be used for proximal femur, unless prohibited (eg, hip implant). If the right side must be used or is inadvertently used at screening, then it must be used consistently throughout the study. Lumbar spine scans should include L1 through L4. At least 2 lumbar vertebrae from L1-L4 must be evaluable by DXA.

After analysis of the scans by the central imaging vendor, the study site may be asked to re-acquire a scan, because of poor positioning or other technical reasons. The investigator sites must comply with the requests from the central imaging vendor.

Detailed instructions for scan acquisition will be in a separate manual provided by the central imaging vendor.

7.3.11 Spine Radiographs

Lateral radiographs of the thoracic and lumbar spine will be obtained at scheduled time-points to determine morphometric fractures. Baseline lateral spine radiographs will be obtained at screening for all subjects, unless an adequate lateral spine radiograph has been obtained within the 2 months prior to screening day; in this case the radiograph must still be sent to the central imaging vendor. All available radiographic assessments for evaluation of potential fracture from screening until end of study will be submitted to the central imaging vendor for final analysis. The results from the central imaging vendor analysis of the scan data will be used for determination of eligibility and analysis of the final dataset.

7.3.12 Radiographs for Assessment of Long-bone Fractures

Long-bone fractures which occurred within 2 years prior to screening should be substantiated by radiographs, where available, or with a medical report, in the event of unavailable radiographs. Images and/or radiologic/medical reports for potential long-bone fractures will be submitted to the central imaging vendor for reading and evaluation.

7.3.13 Knee Radiograph

Anteroposterior (AP) radiographs of both knees (unless prohibited by the presence of hardware such as implants) will be used to calculate the metaphyseal index Z-score of each knee; the score will then be based on the knee with the higher Z-score. The knee for assessment of metaphyseal index during the study should be the 1 with the higher Z-score at day 1, unless prohibited by presence of hardware, in which case an AP radiograph of the contralateral knee may be obtained. Knee radiographs will be submitted to the central imaging vendor for reading and evaluation.

7.3.14 Dental Radiograms

Lateral Cephalogram

The lateral cephalogram is a profile X-ray of the skull and soft tissues and is used to assess the relation of the teeth in the jaws, the relation of the jaws to the skull, and the relation of the soft tissues to the teeth and jaws. Lateral cephalogram will be performed to enable assessment of mandibular shaping.

Panoramic Radiogram

The panoramic radiogram is a panoramic scanning dental X-ray of the upper and lower jaw, which shows a 2-dimensional view of a half-circle from ear to ear. Panoramic radiogram will be performed to monitor molar eruption at day 1 and end of the study.

Other Dental Radiograms

Reflex radiographic assessment (eg, panoramic, bitewing, or periapical view) may be performed in the event a subject is referred to a dentist due to suspicion of unerupted molar(s), based on visual inspection. The choice of technique/view for this reflex radiographic assessment (eg, panoramic, bitewing, or periapical view) will be determined by the dentist based on his/her professional judgment. All films resulting from these assessments should be submitted to the central reader.

7.3.15 Oral Visual Inspection

Each subject will undergo a visual inspection under natural light for the presence of molars. Since third molar eruption normally occurs after age 21, evaluation of third molar eruption will not be carried out.

Oral visual inspection should be performed at the month 12 and 24 visits to assess the risk for unerupted molars. The subject should be referred to a dentist to perform radiographic assessment of the unerupted molar(s) if:

- A subject is 7 years of age or older and less than 13 years of age and appears to have an unerupted upper or lower first molar (ie, all 4 first molars should be visible/detectable)
- A subject is 13 years of age or older and appears to have an unerupted upper or lower (first or) second molar (ie, all 4 first molars and all 4 second molars should be visible/detectable)

7.3.16 Patient-reported Outcomes (PROs)

The subject's health-related quality of life, physical functioning, and pain intensity will be assessed using the CHQ-PF-50, CHAQ, and the WBFPRS.

The CHQ-PF-50 is a generic health-related quality-of-life instrument that is used to measure 14 unique physical and psychosocial domains for children from 5 to 18 years of age; the parent-reported version of the questionnaire is to be used in this study, as summary scoring and norms are not available for the child-reported version. The CHAQ has been developed to measure the physical functioning in children 6 months to 18 years of age. The WBFPRS is a horizontal pain scale for children from 3 to 18 years,

which consists of 6 hand-drawn faces that range from a smiling “no hurt” face with a score of 0 to a crying “hurts most” face with a score of 10.

7.3.17 Pharmacokinetic (PK) Samples

All subjects receiving denosumab will have PK samples assessed. Blood sample(s) for PK testing are to be collected for the measurement of pharmacokinetic concentrations.

7.4 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected for the measurement of antidenosumab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity, and presence of immune complexes. Additional blood samples may be obtained to rule out antidenosumab antibodies during the study.

Sites will be notified of any positive neutralizing antibody results to denosumab or protocol-required therapies. If results are not provided, no neutralizing antibodies to denosumab or protocol-required therapies have been detected.

Subjects who test positive for neutralizing antibodies to denosumab (eg, Amgen or non-Amgen IPs) or protocol-required therapies at the final scheduled study visit will be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) postadministration of denosumab (eg, Amgen or non-Amgen IPs) or protocol-required therapies. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive denosumab or protocol-required therapies.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-denosumab (eg, Amgen or non-Amgen IPs) or protocol-required therapies antibody response may also be asked to return for additional follow-up testing. Refer to the Schedule of Assessments (Table 2), as applicable, for specific time points and the laboratory manual for detailed collection and handling instructions.

7.5 Optional Substudies

[redacted]

7.6 Early Termination

If the subject discontinues the study prior to the month 36 visit, a safety follow-up visit will occur within 30 days following the last protocol-required therapy.

All procedures outlined for the month 36 visit will be performed during this visit with the following exception:

- Procedures involving radiation exposure other than DXA assessment may not be performed if < 3 months have elapsed since the previous radiographic assessment
  - DXA scans will only be performed if > 30 days have elapsed since the previous assessment
- Administration of PROs may not be performed if < 1 month has elapsed since the previous assessment

7.7 Sample Storage and Destruction

Any blood PK sample collected according to the Schedule of Assessments (Table 2) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If permitted by local law and informed consent is provided by the subject's legally acceptable representative(s), Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand GiOP, the dose response and/or prediction of response to denosumab, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of other exploratory studies are not placed in the subject's

medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 2) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints and adverse events. Subjects who have discontinued investigational product and/or protocol-required therapies or procedures should not be automatically removed from the study. Whenever

safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Section 8.3.1 and Section 8.3.2.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Study

8.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

1. Subject request
2. Safety concern due to:
    a. Ineligibility determined
    b. Protocol deviation
    c. Noncompliance
    d. Requirement for alternative therapy

e. Adverse event (but not limited to):
   - Severe or symptomatic hypocalcemia
     - Subjects who are removed from treatment as a result of severe or symptomatic hypocalcemia should receive treatment according to local standard of care, at the discretion of the treating physician and should be closely followed up until resolution of the adverse event
   - Osteonecrosis of the jaw
   - Serious opportunistic infection

3. Decision by sponsor (other than subject request or safety concern)
4. Death
5. Lost to follow-up
6. Pregnancy
7. Other protocol-specified criteria:
   a. $\geq$ 4 new fractures in 6 months
   b. $>$ 2 new long-bone fractures in 6 months
   c. Decline in lumbar spine BMD Z-score by 0.5 units or more in 6 months
      - Subjects who are removed from treatment as a result of criterion a, b, or c (above) should be followed up and treated, if applicable, according to local standard of care, at the discretion of the treating physician
   d. Changes in growth plate morphology, as observed in the 6-month monitoring, considered by the investigator to be unexpected and having an adverse clinical impact for the subject
   h. Disease flare requiring treatment not allowed in the protocol
   i. Dental abnormalities requiring invasive dental procedures
   j. Serious infection, if the subject is receiving a biologic agent for the treatment of underlying inflammatory disease
      - Serious infection is defined as a serious adverse event of infection that is complicated by multiple organ involvement or sepsis
        - Sepsis is defined by the presence of infection and a severe systemic inflammatory response

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

If the severity of an adverse event worsens from onset to resolution, a single event for each increased level of severity should be recorded on the Events eCRF.

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

9.1.2 Serious Adverse Events

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

- Fatal
- 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
- Congenital anomaly/birth defect
- Other medically important serious event

An adverse event would meet the criterion of "requires hospitalization," if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event." Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, DILI (see Appendix A for drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

9.2.1.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product through the end of study are reported using the Events CRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
- Dates of onset and resolution (if resolved);
- Did the event start prior to first dose of investigational product, other protocol-required therapies;
- Assessment of seriousness;
- Severity (or toxicity defined below);
- Assessment of relatedness to investigational product or other protocol-required therapies;
- Action taken; and
- Outcome of event

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events. The grading scale used in this study is described in Appendix A. If the severity of an adverse event worsens from onset to resolution, record a single event for each increased level of severity.

The investigator must assess whether the adverse event is possibly related to the investigational product(s) and/or other protocol-required therapies. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility

that the event may have been caused by the investigational product(s) and/or other protocol-required therapies?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of investigational product, protocol-required therapies, and/or procedure (including any screening procedures). This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of investigational product, protocol-required therapies, and/or procedure)"?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.1.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the dosing interval or end of study, whichever is a longer period, are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Events CRF.

If the electronic data capture (EDC) system is unavailable for more than 24 hours to the site staff to report the serious adverse event, the information is to be reported to Amgen via a paper-based Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event [eSAE] Contingency Report Form) within 24 hours of the investigator's awareness of the event. See Appendix B for a sample of the electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a serious adverse event is reported to Amgen via the eSerious

Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

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

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Events CRF.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Serious adverse event(s) should be reported to Amgen (regardless of causality) if the investigator becomes aware of a serious adverse event.

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.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice (GCP).

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local regulatory requirements and procedures.

9.2.1.3 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.1.4 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Events CRF.

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

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period (as defined in Section 9.2.1.1) or after end of study. However, these serious adverse events should be reported to Amgen (regardless of causality) if the investigator becomes aware of them. In some countries (eg, European Union member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

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

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking denosumab report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur within 5 months after the last dose of Amgen investigational product.

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

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

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

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

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

Change from baseline in lumbar spine BMD Z-score as assessed by DXA at 12 months.

10.1.1.2 Secondary Endpoint(s)

- Change from baseline in lumbar spine BMD Z-score as assessed by DXA at 6, 18, 24, and 36 months
- Change from baseline in proximal femur BMD Z-score as assessed by DXA at 6, 12, 18, 24, and 36 months
- Subject incidence of X-ray confirmed long-bone fractures and new and worsening vertebral fractures **during** 12, 24, and 36 months

- Subject incidence of improving vertebral fractures at 12, 24, and 36 months compared to **baseline**
- Subject incidence of **new** and **worsening** vertebral and nonvertebral fractures **during 12, 24, and 36 months**
- Change from baseline in CHQ-PF-50 Physical Summary Score at 12, 24, and 36 months
- Change from baseline in CHQ-PF-50 Psychological Summary Score at 12, 24, and 36 months
- Change from baseline in CHAQ Disability Index Score at 12, 24, and 36 months
- Change from baseline WBFPRS at 12, 24, and 36 months
- Change from baseline in growth velocity, determined by calculating age-adjusted Z-scores for height, weight, and BMI, at 12, 24, and 36 months
- Serum concentration of denosumab at 1, 10, and 30 days, and 3, 6, 12, and 18 months

10.1.1.3 Exploratory Endpoint(s)

[redacted]

10.1.1.4 Safety Endpoints

- Subject incidence of adverse events and serious adverse events
- Change from baseline in laboratory values
- Change from baseline in vital signs
- Subject incidence of antidenosumab antibodies

10.1.2 Analysis Sets

10.1.2.1 Full Analysis Set

The full analysis set (FAS) is defined according to the intent-to-treat analysis to include all subjects enrolled into the study.

10.1.2.2 Primary DXA Analysis Set

The primary DXA analysis set includes all subjects in the FAS **with baseline** and will **≥ 1 post-baseline lumbar spine provided by the central imaging vendor during the first 12 months and** only be used to analyze the change from baseline in lumbar spine BMD Z-score as assessed by DXA at 12 months, as the primary analysis for the primary efficacy endpoint. Subjects will be analyzed according to their randomized treatment group.

10.1.2.3 DXA Analysis Set

The DXA analysis set for each endpoint of interest (lumbar spine, total hip or femoral neck) includes all subjects in the FAS with baseline and ≥ 1 post baseline valid DXA assessments as provided by the central imaging vendor for the relevant endpoint at or before the timepoint under consideration (6, 12, 18, 24 or 36 months). Subjects will be analyzed according to their randomized treatment group.

10.1.2.4 Vertebral Fracture Analysis Set

For each time point of interest (at 12, 24 and 36 months), the vertebral analysis set includes all subjects in the FAS who have a non-missing baseline and ≥ 1 non-missing postbaseline X-ray vertebral evaluation as provided by the central imaging vendor, on or before the time point under consideration. This analysis set will be used to analyze incidence of vertebral fracture.

10.1.2.5 Nonvertebral Fracture Analysis Set

The nonvertebral fracture analysis set includes all subjects in the FAS, and will be used to analyze the subject incidence of nonvertebral fracture endpoints. All fractures will be identified or confirmed by the central imaging vendor.

10.1.2.6 PRO Analysis Set

For each PRO (CHQ-PF-50, CHAQ disability index score and WBFPRS), the PRO analysis set includes all subjects in the FAS with baseline and at least 1 postbaseline valid PRO response for the appropriate PRO at the time point under consideration. Note that this subset could potentially be different from endpoint to endpoint, and from time point to time point, due to missing data.

10.1.2.7 Growth Velocity Analysis Set

For each growth velocity endpoint (weight-for-age, height-for-age, and BMI-for-age Z-scores) and time point (12, 24 and 36 months), the analysis set includes all subjects in the FAS who have the relevant data (age in total months, weight, height, and BMI, respectively) at baseline, and on or before the time point of interest.

10.1.2.8 Safety Analysis Sets

The safety analysis set for the treatment phase includes all subjects in the FAS who received ≥ 1 dose of investigational product. The safety analysis set for the observation period includes all subjects who completed the treatment phase and remain in the observation phase.

10.1.2.9 PK Analysis Set

The PK analysis set includes all subjects in the FAS who have ≥ 1 serum denosumab reported result.

[redacted]

10.1.3 Covariates and Subgroups

10.1.3.1 Covariates

The following covariates are assumed to have prognostic value with respect to the lumbar spine BMD Z-score as assessed by DXA. The covariate's association with the primary endpoint might be investigated.

- Sex (Male/Female)
- Race (White, non-White)
- Age (years)
- Baseline lumbar spine BMD Z-score
- Baseline glucocorticoid dose

10.1.4 Handling of Missing and Incomplete Data

Subjects may have missing specific data points for a variety of causes. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or non-evaluability of a specific clinical measurement at its planned clinical visit. Missing data will not be imputed for this study.

10.2 Sample Size Considerations

The study will enroll 24 subjects. Assuming that approximately 10% of subjects will not be evaluable at month 12 for the primary efficacy endpoint due to dropout, the analysis set for the primary efficacy endpoint will include approximately 20 subjects.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded at the final analysis. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded at the final analysis, except as specified (eg, Section 5.3 and Section 9.2.1.2).

Individual subject treatment assignments will be maintained by the IVRS/IWRS. Any unplanned unblinding occurring during the study period will be documented and reported in the final clinical study report. The Independent Data Monitoring Committee (DMC) members and the Independent Biostatistical Group will have access to the treatment assignments and subject level data from the clinical trial database. Amgen staff members who are involved in randomization, biological sample management, performing PK and anti-denosumab antibody assay analysis will have treatment assignment information but will not have access to the subject level data from the clinical database.

10.4 Planned Analyses

10.4.1 Interim Analyses

No interim analysis is planned for the study.

10.4.2 Data Monitoring Committee (DMC)

An external, independent DMC will be used to oversee progress of the study and make recommendations relating to early closure/extension or alteration of the study based on ongoing monitoring of the study data. The DMC will be comprised of members external to Amgen. The DMC members will have access to treatment assignments in order to monitor safety and efficacy results to protect subjects. To minimize the potential introduction of bias, the DMC members will not have any direct contact with the study team, site personnel, or subjects. An independent statistical service provider will generate unblinded reports for review by the DMC. If at any time there are safety concerns, the DMC will communicate the concerns to a representative from Amgen senior management. A charter specifying the DMC functions will be written with the agreement of the DMC members. **Last DMC was in March 2022 as all subjects have completed 12-month double blind treatment period of the study.**

10.4.3 Primary Analysis

The primary analysis will be conducted at the time of the final analysis.

10.4.4 Final Analysis

The final analysis for the study, including the analysis of the primary endpoint, will be performed when all enrolled subjects have had the opportunity to complete the 36-month follow-up.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Descriptive statistics will be provided for demographics and subject characteristics, efficacy, PROs, and safety data. Descriptive statistics of continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using counts and percentages.

10.5.2 Primary Efficacy Endpoint

The change from baseline in lumbar spine BMD Z-score at 12 months will be analyzed based on the primary DXA analysis set using an analysis of covariance (ANCOVA) model including treatment (denosumab vs placebo), baseline age (age at informed consent), and baseline BMD Z-score. Missing baseline and postbaseline BMD Z-scores will not be imputed. The superiority of denosumab compared to placebo for the primary efficacy endpoint will be estimated from the 12-month least-squares (LS) mean of the treatment difference (denosumab – placebo) and the corresponding 95% confidence interval.

A sensitivity analysis of the primary efficacy endpoint will be conducted in the DXA analysis set, in subjects with baseline and ≥ 1 postbaseline valid DXA assessments, using a repeated measures analysis. Treatment (denosumab vs placebo), study visit (6, and 12 months), baseline age, baseline BMD Z-score, will be included as fixed effects, and treatment-by-visit included as an interaction. Study visit will be treated as a categorical variable. The 12-month LS mean of the treatment difference (denosumab – placebo) and the corresponding 95% confidence interval and associated p-value will be estimated. Unstructured variance–covariance structure will be used for estimation in the repeated measures analysis. Other variance-covariance structure may be substituted if convergence problem arises.

10.5.3 Secondary Efficacy Endpoint(s)

Secondary efficacy endpoints will be assessed without multiplicity adjustment.

10.5.3.1 Other Change From Baseline in BMD Z-score by DXA

For each skeletal site (lumbar spine, total hip, and femoral neck), change from baseline in BMD Z-score will be analyzed using the same repeated measures analysis as described for the sensitivity analysis of the primary efficacy endpoint in Section 10.5.2.

10.5.3.2 New and Worsening Vertebral Fractures, and Nonvertebral Fractures

The subject incidence of new and worsening vertebral fractures, and nonvertebral fractures will be summarized by treatment group.

10.5.3.3 Improved Vertebral Fracture

The proportion of subjects with improved vertebral fracture will be summarized at each time point based on the vertebral fracture analysis set.

10.5.3.4 Patient Reported Outcomes

Patient reported outcomes (CHQ-PF-50, CHAQ disability index score, and WBFPRS) and their changes from baseline will be summarized at 12, 24, and 36 months based on their respective PRO analysis set. There is no imputation for missing baseline or postbaseline data.

10.5.3.5 Growth Velocity

Change from baseline in age-adjusted growth velocity endpoints will be summarized at 12, 24, and 36 months based on the growth velocity analysis set. There is no imputation for missing data.

10.5.3.6 Serum Denosumab Concentrations

Individual serum denosumab concentration-time data will be tabulated and presented graphically based on the PK analysis set. A mean concentration-time profile will also be provided. There will be no imputation for missing values.

[redacted]

10.5.4 Safety Endpoints

All safety endpoints will be analyzed separately for the **12-month double-blind period, 24-month** treatment **period** and **overall study period (36-month)**.

10.5.4.1 Adverse Events

All adverse events will be summarized based on the respective safety analysis set. Subject incidence of all treatment-emergent adverse events and serious adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, adverse events leading to withdrawal from investigational product and treatment-emergent adverse events of interest will also be provided.

10.5.4.2 Clinical Laboratory Measurements

Actual values and changes from baseline in each parameter will be descriptively summarized at each visit. For serum albumin-adjusted calcium, phosphorus, and ALP, summary of the percent change from baseline also will be provided.

Shifts in laboratory parameters between baseline and the most extreme postbaseline values will be assessed based on the Common Terminology Criteria for Adverse Events v 4.0.

All laboratory analyses will be based on the safety analysis set. Subjects with missing data for a scheduled visit will not contribute to the tabulation for that time point (no imputation).

10.5.4.3 Vital Signs

Descriptive statistics of the actual values and changes from baseline in vital signs (heart rate, respiration rate, temperature) will be presented by visit based on the safety analysis set. Subjects with missing data for a scheduled visit will not contribute to the tabulation for that time point (no imputation).

10.5.4.4 Antidenosumab Antibodies

The incidence and percentage of subjects who develop antidenosumab antibodies (binding and, if positive, neutralizing) at any time will be tabulated based on the safety analysis set.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Manager to the investigator. The written ICF is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product(s) is/are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed consent form is to 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 ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood.

In this study, obtaining assent from the child and consent from the parents or legally authorized representative, except if the child is very young, as defined by local law will apply. A child is defined as a person who has not attained the legal age for consent for treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will take place. The local IRB/IEC will determine the process for obtaining and documenting the assent process for pediatric subject, but should follow the guidelines established by the Department of Health and Human Services Office of Human Research Protections guidelines, which state an explanation of the procedures involved in the study should be made in a language appropriate to the child's age, experience, maturity, and condition.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/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 is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of signing of informed consent.
- For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental/International Conference on Harmonisation GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/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 such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- 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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. After Amgen amends the protocol, the investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/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 Amgen investigational product(s) by an 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 Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

12.2 Study Documentation and Archive

The investigator is to 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 CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF 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.

In this study, the IVR/IWR system captures the following data points and these are considered source data: subject identification number, randomization date, randomization number, and treatment group assignment.

CRF entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data). In this study, PROs may be considered as source documents.

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.

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

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative(s) 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, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor is responsible for verifying the CRFs 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 Clinical Monitor is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the Clinical Monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with International Conference on Harmonisation GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research & Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, International Conference on Harmonisation GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail."
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database. Self-evident corrections will be documented in the CRF Standard Instructions and the CRF Specific Instructions, both of these will be available through the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit, [eg, week 4 and early termination]) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 2), the investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

CRFs must be completed in English. TRADENAMES® (if used) 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.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

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

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

Additional information on the current guidelines for publications can be found at the following location: http://www.icmje.org/.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

During the study, the subjects may be reimbursed for reasonable expenses associated with the study (eg, transportation), if permitted under applicable regional laws or regulatory guidelines. These arrangements for compensation are described in the Informed Consent that is available as a separate document.

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events is available at the following location:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.4 require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Events eCRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.1.3.

Additional Clinical Assessments and Observation

All subjects in whom investigational product or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI (Section 6.4.1) or who experience AST or ALT elevations > 3 x ULN (except for subjects with dystrophinopathies) are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR as clinically necessary until laboratory abnormalities improve.
- Obtain pediatric gastroenterologist or pediatric hepatologist consult
  - The diagnostic approach (including blood tests) to investigate alternative causes for abnormal liver tests is to be determined in consultation with a pediatric gastroenterologist or hepatologist.
- The "close observation" is to continue until all laboratory abnormalities return to baseline or normalize and subject's clinical condition improves.

The potential DILI event and additional information such as medical history, concomitant medications, clinical presentation, and laboratory results must be captured in corresponding eCRFs.

Appendix B. Sample Electronic Serious Adverse Event Contingency Report Form

AMGEN
Study # 20140444
Denosumab

Electronic Serious Adverse Event Contingency Report Form
For Restricted Use

Reason for reporting this event via fax
The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *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	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? Denosumab No✓	Denosumab Yes✓	<Pldevice> No✓	<Pldevice> Yes✓	<Pldevice> No✓	<Pldevice> Yes✓	<Pldevice> No✓	<Pldevice> Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

		Prior to, or at time of Event: Date of Initial Dose Day Month Year	Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
IP/Amgen Device:								
Denosumab	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20140444 Denosumab	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test / Unit											

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

AMGEN Study # 20140444 Denosumab	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A PAGE

1. Case Administrative Information

Protocol/Study Number: 20140444

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: [redacted] Date: _____

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Amendment 4

Protocol Title: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Safety and Efficacy of Denosumab in Pediatric Subjects With Glucocorticoid-induced Osteoporosis

Amgen Protocol Number: 20140444

NCT Number: NCT03164928

Amendment Date: 10 July 2023

Rationale:

The protocol has been amended to remove specific endpoints that will not be met for end of study and to align with European Medicines Agency/Paediatric Committee (EMA/PDCO) Modification Summary Report provided by the EMA. Changes including, but not limited to, the following are being incorporated into the protocol:

- Updated secondary objectives and endpoints:
    - Replaced “from pre-treatment to post-treatment” with “compared to baseline” to clarify that the determination of improving vertebral fracture is to compare with baseline spine X-ray.
    - Removed language ‘overall among subjects with clinical fracture reduction, and among subjects with clinical fracture increase’ as it is not statistically meaningful to perform a subgroup analysis in a study that has only enrolled globally 24 subjects.
    - Updated language to clarify that new and worsening vertebral and nonvertebral fractures will be used to evaluate the effect of denosumab in children with Glucocorticoid (GC)-induced osteoporosis (GiOP).
- Updated Section 1.3: Safety to delete the evaluation of metaphysical index and Molar eruption and mandibular shaping.
- Added footnote q stating that after the protocol required reporting period or after end of study, serious adverse events will be reported to Amgen.
- Added language to Section 2.3.2 to clarify that pediatric patients with osteogenesis imperfecta, severe life threatening adverse events of

hypercalcemia have been reported at or near the end of the denosumab 1 mg/kg Q3M dosing period (> 60 days from the previous dose) in Study 20130173.

- Updated language in Section 10.4.2 to clarify that the last data management committee was in March 2022 as all subjects have completed 12-month double blind treatment period of the study.
- Updated language in Section 10.5.2 to add additional language on sensitivity analysis of the primary efficacy endpoint.
- Updated language in Section 10.5.4: Safety endpoints to clarify that safety endpoints will be analyzed for the 12-month double-blind period, 24-month treatment period and overall study period (36-month).
- Removed Abnormal Metaphyseal Index Z score, Abnormal Molar Eruption, and Abnormal Mandibular Shaping Section 10.5.4.5.
- Administrative, typographical, abbreviations, and formatting changes were made throughout the protocol.

Amendment 3

Protocol Title: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Safety and Efficacy of Denosumab in Pediatric Subjects With Glucocorticoid-induced Osteoporosis

Amgen Protocol Number (Denosumab/Prolia®) 20140444

EudraCT number 2016-003083-39

NCT number NCT03164928

Amendment Date: 20 April 2021

Rationale:

The following changes were made to the protocol dated 20 April 2021.

- Updated the number of subjects enrolled in the study.
  - The study was initially designed to enroll 150 patients, to attain at least 100 evaluable patients for the primary analysis and has been running since June 2017; however, as of December 2020, only 24 patients have been enrolled at 36 clinical sites activated globally.
  - Following agreement from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), Amgen made a decision to end enrollment into this study. The primary reason to request FDA and EMA agreement for early discontinuation is that there are too few children with the disease or condition to study, and this is not due to safety or efficacy concerns. In order to maximize the value of the data from this study in this rare pediatric population, subjects who have been enrolled in the study will be allowed to complete the study, as defined in the protocol (ie, to last visit at 36 months). As of January 2021, enrolment of subjects into this study has been closed. The study is anticipated to end when the remaining subjects will have reached the 36 months visit.
- Aligned the protocol with current Amgen protocol template and safety reporting language.
- Administrative and editorial changes were completed as part of this amendment.

Amendment 2

Protocol Title: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Safety and Efficacy of Denosumab in Pediatric Subjects With Glucocorticoid-induced Osteoporosis

Amgen Protocol Number 20140444

EudraCT number 2016-003083-39

NCT number NCT03164928

Amendment Date: 25 May 2018

Rationale:

The major purpose of this protocol amendment is to reflect changes in protocol 20140444 arising as a result of recommendations from FDA protocol-review in conjunction with the Prolia iPSP application, changes to the matching placebo formulation, and administrative changes. Revisions include:

- Protocol synopsis edited to increase clarity and align with changes to the main protocol sections
- Asia and the Middle East were added as study site continents to assist patient enrollment
- Language added to clarify the meaning of exclusion criteria 240 and 241
- Eligibility criteria 205 added in response to FDA suggestion
- Schedule of assessments updated to include blood sampling for immunogenicity assessments at months 1, 3, and 6
- Detailed instructions provided for height measurement added, at FDA suggestion
- Rescreening period without re-consent requirement changed to 30 days throughout for consistency
- Changes in rules for adverse event reporting if the severity changes, to align with TA program conventions
- Updates to Pregnancy and Lactation reporting section per new regulatory requirements
- Clarify age recording rules in the CRF demographics page
- Add description of additional sensitivity analysis to asses impact of short stature on BMD Z-scores in response to FDA comments
- Decription of placebo was changed to reflect the fact that with the new XGEVA formulation, the placebo will no longer be identical in composition
- Text was edited in sections 2.3 and 2.4 to reflect the completion of Study 20101217
- Minor administative changes and clarification was made throughout the document

Approved

Amendment 1

Protocol Title: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Safety and Efficacy of Denosumab in Pediatric Subjects With Glucocorticoid-induced Osteoporosis

Amgen Protocol Number 20140444

Amendment Date: 14 February 2017

Rationale:

The purpose of this protocol amendment is to reflect changes in the design of protocol 20140444 arising from concerns around the acceptability and feasibility of subject exposure to placebo for 24 months. Major changes include:

- Subjects in the placebo arm will transition to open-label denosumab at 12 months and continue open-label denosumab for an additional 12 months.
- Secondary objectives and endpoints have been updated to reflect the change in placebo duration.
- The study schema has been updated to reflect these revisions.

Statistical revisions:

- The primary analysis will be conducted at the time of the final analysis.
- To remain in alignment with the key binding elements in the current PIP (Decision P/0058/2016), the primary analysis has been updated to use an analysis of covariance (ANCOVA) model, replacing the repeated measures analysis. The repeated measures analysis has now been included as a sensitivity analysis.
- Following current guidelines on handling of missing data, the protocol has been updated to include imputation rules for analysis of the primary endpoint.

Other revisions:

- Language added to clarify the end of study date.
- Language regarding the reasons for stopping Amgen investigational product has been reorganized to ensure the reasons are mutually exclusive.

Approved

- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) has been removed from the list of acceptable forms of contraception as it is a prohibited medication for the study.
- Language regarding collection of medical and medication history clarified
- Examples of underlying disease types requiring treatment with systemic glucocorticoids have been added.
- Minor administrative changes and clarifications have also been incorporated.

Approved