Title: Prospective, Multicenter, Single-arm Study to Evaluate Efficacy, Safety, and Pharmacokinetics of Denosumab in Children With Osteogenesis Imperfecta

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Amendment 7	**22 October 2021**
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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 (International Council for Harmonisation [ICH] E6).

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Investigator's Agreement

I have read the attached protocol entitled Prospective, Multicenter, Single-arm Study to Evaluate Efficacy, Safety, and Pharmacokinetics of Denosumab in Children With Osteogenesis Imperfecta, dated **26 November 2021**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on 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 subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one 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: Prospective, Multicenter, Single-arm Study to Evaluate Efficacy, Safety, and Pharmacokinetics of Denosumab in Children With Osteogenesis Imperfecta

Study Phase: 3

Indication: Treatment of osteogenesis imperfecta (OI) in children 2 to 17 years of age

Primary Objective: To evaluate the effect of denosumab **i**n lumbar spine bone mineral density (BMD) Z-score at 12 months, as assessed by dual-energy X-ray absorptiometry (DXA), in children 2 to 17 years of age (at the time of screening) on a 3-Month Dosing Regimen with OI.

Secondary Objective(s): To evaluate denosumab in children 2 to 17 years of age (at the time of screening) with OI on a 3-Month Dosing Regimen with respect to:

- Change in lumbar spine BMD Z-score, as assessed by DXA, at 6 months
- Change in proximal femur BMD Z-score, as assessed by DXA, at 6 and 12 months (in subjects 5 years of age and older)
- Incidence of X-ray confirmed long bone and new and worsening vertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Incidence of X-ray confirmed new and worsening vertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Incidence of X-ray confirmed new vertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Incidence of X-ray confirmed improving vertebral fractures from **baseline of 3-**Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Incidence of vertebral and nonvertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen (in subjects 5 years of age or older)
- Change in Child Health Questionnaire-Parent Form-50 (CHQ-PF-50) Physical Summary score at 12 months
- Change in CHQ-PF-50 Psychological Summary score at 12 months
- Change in Childhood Health Assessment Questionnaire (CHAQ) Disability Index score at 12 months
- Change in Wong-Baker Faces Pain Rating Scale (WBFPRS) at 12 months
- Change in growth velocity (determined by calculating age-adjusted Z-scores for height, weight, and body mass index [BMI]) at 12 months
- Serum denosumab concentration and bone turnover markers (BTM) collected **at 1,** 10, 30, and 60 days after the first dose of 3-Month Dosing Regimen and every 3 months in all subjects

Exploratory Objectives: [redacted]

Safety Objectives:

To evaluate denosumab in children 2 to 17 years of age (at the time of screening) with OI on a 3-Month Dosing Regimen or 6-Month Dosing Regimen with respect to:

- Adverse events and serious adverse events
- Laboratory parameters
- Vital signs
- Antidenosumab antibodies
- Metaphyseal index
- Molar eruption and mandibular shaping
- Hypercalcemia

Hypotheses: The hypothesis of the study is that the change from baseline in lumbar spine BMD Z-score following 12 months of denosumab treatment with 3-Month Dosing Regimen in children 2 to 17 years of age (at the time of screening) with OI will be greater than that from historical control (ie, placebo or untreated subjects) (Letocha et al, 2005; Rauch et al, 2009; Ward et al, 2011) which was estimated to be 0.01 (95% CI: -0.17, 0.18).

Primary Endpoint: Change from baseline in lumbar spine BMD Z-score, as assessed by DXA, at 12 months in subjects receiving the 3-Month Dosing Regimen

Secondary Endpoint(s):

- Change from baseline in lumbar spine BMD Z-score, as assessed by DXA, at 6 months in subjects receiving the 3-Month Dosing Regimen
- Change from baseline in proximal femur BMD Z-score, as assessed by DXA, at 6 and 12 months (in subjects 5 years of age and older) in subjects receiving the 3-Month Dosing Regimen
- Incidence of X-ray confirmed long bone and new and worsening vertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Incidence of X-ray confirmed new and worsening vertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Incidence of X-ray confirmed new vertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Subject incidence of improving vertebral fractures from **baseline of 3-**Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Incidence of vertebral and nonvertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen (in subjects 5 years of age or older)
- Change from baseline in CHQ-PF-50 Physical Summary score at 12 months in subjects receiving the 3-Month Dosing Regimen
- Change from baseline in CHQ-PF-50 Psychological Summary score at 12 months in subjects receiving the 3-Month Dosing Regimen
- Change from baseline in CHAQ Disability Index score at 12 months in subjects receiving the 3-Month Dosing Regimen
- Change from baseline in WBFPRS at 12 months in subjects receiving the 3-Month Dosing Regimen
- Change from baseline in growth velocity (determined by calculating age-adjusted Z-scores for height, weight and BMI) at 12 months in subjects receiving the 3-Month Dosing Regimen
- Serum concentration of denosumab and serum BTM on days 1, 10, 30, 60, and every 3 months in subjects on 3-Month Dosing Regimen

Exploratory Endpoints:

[redacted]

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
- Subject incidence of metaphyseal index Z-score above age-appropriate normal range
- Subject incidence of abnormal molar eruption
- Subject incidence of abnormal mandibular shaping
- Subject incidence of hypercalcemia

Study Design Update:

As of 30 September 2021, due to the life-threatening risk of hypercalcemia, subjects on study who had not completed their End of Study (EOS) visit were immediately discontinued from IP, and will be followed for safety for 24 weeks following the last dose of IP per the updated Schedule of Assessments (Table 7-5). The last dose of IP will be considered week 0. Subjects who have been on alternative therapy for more than 6 months or whose last dose of IP was greater than 24 weeks, no additional 24-week safety follow-up is required. These subjects can follow the previous protocol (protocol amendment 6) and complete the EOS Case Report Form (CRF). Subjects whose last dose was between 12 and 24 weeks ago can complete the EOS assessments at week 24 per the updated Schedule of Assessments (Table 7-5).

6-Month Dosing Regimen

This is a prospective, multicenter, single-arm study in children 2 to 17 years of age with OI. Approximately 150 subjects will be enrolled including at least 30 subjects less than 7 years of age (at time of initial enrollment). All subjects will receive denosumab 1 mg/kg (up to a maximum of 60 mg) given subcutaneously every 6 months for 36 months. Enrollment will be gated as below:

1. Five subjects 11 to 17 years of age (sentinel cohort) will be initially enrolled in the trial. After they complete 14 days of mineral homeostasis monitoring, enrollment will be open to the remainder of the 11 to 17 years-of-age cohort.
2. After the first 5 subjects 11 to 17 years of age enrolled have been treated for 12 months, enrollment will be opened to children 7 to 10 years of age
3. After the first 5 subjects 7 to 10 years of age enrolled have been treated for 6 months, enrollment will be opened to children 2 to 6 years of age

At least 30 subjects less than 7 years of age (at time of initial enrollment) will be enrolled.

3-Month Dosing Regimen

Sixty previously enrolled subjects **were transitioned** to a 3-Month Dosing Regimen, among them approximately 20 subjects younger than 7 years of age (at time of initial enrollment**). Per urgent safety measure, a decision has been made to stop treatment and subjects will continue a 24-week safety follow up period. Following implementation of this urgent safety measure and requirement for subjects to follow up for 24 weeks after last dose of denosumab, the maximum duration of this regimen could be up to 51 months (84 weeks).**

Sample Size: Approximately **153** subjects **have been** enrolled. No additional subjects will be enrolled into this study. **Prior to the implementation of the urgent safety measure, s**ubjects who previously ended treatment but remain**ed** on study **were** eligible to transition to the 3-Month Dosing Regimen unless they ended treatment due to an adverse event. Subjects **also had** the option to either consent to the 3-Month Dosing Regimen or to end study participation.
Sixty subjects have been transitioned to a 3-Month dosing regimen. Starting from 30 September 2021, all dosing has been stopped.

Summary of Subject Eligibility Criteria: **No further subjects were enrolled.** Eligibility criteria relates to initial enrollment into this study (6-Month Dosing Regimen). Subjects reconsenting to a 3-Month Dosing Regimen will not repeat eligibility assessments; however, any subjects who previously ended investigational product (IP) who are receiving alternative therapies must discontinue these before resuming treatment with denosumab.

Inclusion Criteria

- Informed consent (to be provided by parent or legal guardian) and informed assent (to be provided by subjects when age-appropriate).
- Children 2 to 17 years of age inclusive at screening
- Clinical diagnosis of OI defined as a clinical history consistent with type I-IV OI as determined by presence of expected phenotype (examples include: facial shape, voice, blue sclera, dentinogenesis imperfecta, typical radiographic features,

fracture pattern) and lack of additional features unrelated to type I-IV OI (eg, blindness, mental retardation, neuropathy, craniosynostosis, premature exfoliation of deciduous teeth)
  - If familial, also must be autosomal dominant
- Clinical severity of OI as defined by
  - 2 or more prevalent vertebral compression fractures; OR
  - 1 prevalent vertebral compression fracture and 1 or more nonvertebral fractures within the previous 2 years; OR
  - 3 or more fractures within the previous 2 years

Exclusion Criteria

Subjects meeting any of the following criteria at screening are not eligible for enrollment:

- Inability or unwillingness to comply with the requirements for frequent calcium and phosphorus monitoring for 14 days after the first dose of denosumab (only applies to the first 5 subjects 11 to 17 years of age enrolled in the study and the first 5 subjects of any age meeting the criteria for increased bone turnover, see Section 2.3.2.1)
- Currently unhealed fracture or osteotomy as defined by orthopedic opinion
- Osteotomy within 5 months prior to screening
- Evidence of untreated oral cavities or oral infections
- Recent or planned invasive dental procedure
- Surgical tooth extraction which has not healed by screening
- History of an electrophoresis pattern inconsistent with type I to IV OI
- History of known mutation in a gene other than collagen type I alpha 1/collagen type I alpha 2 (COL1A1/COL1A2) causing OI or other metabolic bone disease
- Abnormalities of the following per central laboratory reference ranges at screening:
  - Serum albumin-corrected calcium < lower limit of normal (LLN)
  - Serum vitamin D < 20 ng/mL; rescreening for Vitamin D level < 20 ng/mL will be allowed, after adequate supplementation
  - Aspartate aminotransferase (AST), alanine aminotransferase (ALT) > 1.5 x upper limit of normal (ULN)
  - Total bilirubin (TBL) > 1.5 x ULN (subjects with Gilbert syndrome are eligible)
  - Serum phosphorus < LLN
  - Serum alkaline phosphatase > 20% above the ULN or > 20% below the LLN
- Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (calculated by the Schwartz equation at screening)
- Evidence of any of 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
  - Current, uncontrolled hypercalcemia (albumin-corrected serum Ca > 10% ULN)
  - History of osteomalacia or rickets (chart review)
  - Other bone diseases that affect bone metabolism (eg, osteoporosis pseudoglioma syndrome, idiopathic juvenile osteoporosis, osteopetrosis, hypophosphatasia)
  - History of autoimmune disease
  - History of malabsorption (in children with serum albumin < LLN, malabsorption should be clinically ruled out by the investigator to confirm eligibility)

  - History of rare hereditary problems of fructose intolerance
  - History of long QT syndrome
  - History of non-healing osteotomy
  - History of malignancy
  - History of alcohol or drug abuse
  - History of any solid organ or bone marrow transplant
  - Contraindicated or poorly tolerant of denosumab therapy
- Positive blood screen for human immunodeficiency virus (HIV) -1 or -2 antibody
- Positive blood screen for hepatitis B surface antigen or hepatitis C antibody
- Currently pregnant or planning a pregnancy during the study and for an additional 5 months after the last dose of IP **(**denosumab)
- Currently breastfeeding or planning on breastfeeding during the study and for an additional 5 months after the last dose of IP (denosumab)
- 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 IP (denosumab)
- Received other osteoporosis treatment or bone active treatment with the following guidelines:
  - Prior treatment with
    - denosumab
    - fluoride or strontium for bone disease (fluoride taken for routine dental care is permitted)
    - parathyroid hormone (PTH) or PTH derivatives within 12 months prior to screening
    - zoledronic acid within 6 months prior to screening
    - oral bisphosphonates or intravenous bisphosphonates other than zoledronic acid if the first dose of denosumab would be before their next scheduled bisphosphonate dose would have been given
  - Administration of systemic glucocorticoids (≥ 5.0 mg prednisone equivalents/day for more than 10 days) within 3 months prior to screening. Topical and inhaled glucocorticoids will be allowed
  - Administration of any of the following treatment within 3 months prior to screening:
    - Growth hormone (subjects on stable dose of growth hormone for at least 3 months prior to screening will be allowed)
    - Calcitonin
    - Cathepsin K inhibitor
    - Other bone active drugs including anticonvulsants (except gabapentin and benzodiazepines) and heparin
    - Chronic systemic ketoconazole, androgens, adrenocorticotropic hormone (ACTH), cinacalcet, aluminum, lithium, protease inhibitors, gonadotropin-releasing hormone agonists
- Received Immunosuppressant therapy other than glucocorticoids
- Anticipated major skeletal surgery (eg, rodding surgery, spinal surgery) within the next 12 months from day 1
- Symptoms associated with skull abnormalities such as basilar invagination, basilar impression or Chiari malformation (eg, headache induced by coughing or straining for stool, or parasthesias or weakness)
- Rodding surgery within 5 months prior to screening or not yet healed per orthopedic surgeon
- Spinal fusion surgery within 5 months prior to screening or not yet healed per orthopedic surgeon
- Inability to consume milk
- Planned orthopedic surgery that, in the opinion of the principal investigator, would require missing any dose of IP in year 1 or 2 or more doses thereafter

- Currently receiving treatment in another investigational drug study, or less than 30 days since ending treatment on another investigational drug study(s), or current or planned participation in a clinical trial that would preclude compliance with study requirements
- Other investigational procedures while participating in this study are excluded
- Known intolerance to calcium or vitamin D supplements
- 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's safety or interfere with the study evaluation, procedures or completion
- Subject will not be available for protocol-required study visits, 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

For a full list of eligibility criteria, please refer to Section 4.1.

Investigational Product

Amgen Investigational Product Dosage and Administration: See Section 6.2.1

Denosumab at a dose of 1 mg/kg (up to a maximum dose of 60 mg) will be administered subcutaneously once every 3 months in the 3-Month Dosing Regimen.

Non-investigational Product

Non-Amgen Non-investigational Product Dosage and Administration: All subjects will receive daily supplements. Recommended dose of calcium in this population is 30-50 mg/kg per day to a maximum of 1000 mg elemental calcium. Sites will monitor for potential hypercalcemia and hypercalciuria and other intolerance to supplements and may change dose at investigator discretion. At least 800 IU vitamin D is recommended for the duration of the study with investigator discretion as above.

Procedures: Procedures conducted at baseline, day 1, 3-Month Dosing Regimen day 1, and periodic intervals throughout the study include collection of demographic information and medical and medication history. Dual-energy X-ray absorptiometry assessment of lumbar spine and proximal femur; X-ray radiographic assessment of the spine (thoracic and lumbar); X-ray radiographic assessment of the knees in those with open growth plates who do not have bilateral hardware; dental X-ray (cephalogram and panoramic radiograph); X-ray assessment of unerupted molars; and administration of subject questionnaires (CHQ-PF-50, CHAQ disability score and WBFPRS). Blood will be collected for routine chemistry, hematology, serology, serum 25 (OH) vitamin D, serum concentration of denosumab, BTM (BSAP and sCTX) and antidenosumab antibody assessments. Serum calcium levels will be monitored more frequently in the first 5 subjects enrolling in the study, as well as in the first 5 subjects of any age who meet pre-defined criteria for high bone turnover. During 3-Month Dosing Regimen serum and urine calcium are monitored as per Schedule of Assessments.

Potential events of osteonecrosis of the jaw (ONJ) will be adjudicated by an independent adjudication committee. An external, independent Data Monitoring Committee (DMC) will be used to oversee the 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 all study data in order to monitor safety results to protect subjects, as specified in the DMC charter. Responses to additional ad hoc requests also will be provided. To minimize the potential introduction of bias, the DMC members will not have any direct contact with the study site personnel or subjects.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Section 7.1).

Statistical Considerations: Descriptive statistics will be provided for baseline characteristics, efficacy, patient-reported outcomes (PROs), and safety data. Descriptive statistics on continuous

measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using counts and percentages. Subgroup analysis may be conducted depending on the number of subjects in each subgroup. For the primary endpoint, change from baseline of 3-Month Dosing Regimen in lumbar spine BMD Z-score at 12 months will be analyzed based on all subjects with baseline and at least 1 postbaseline assessment and with validated normative ranges, using repeated measures analysis with visit, age, and baseline BMD Z-score as fixed effects. The visit will be treated as a categorical variable, and there will be no imputation for missing data.

This estimated least squares (LS) mean change at 12 months will be presented with a 95% CI and will be compared to weighted estimated mean (SE) of 0.01 (0.09) from historical controls (Letocha et al, 2005; Rauch et al, 2009; Ward et al, 2011) using a 1-sample two-sided t-test.

The incidence of fractures will be summarized **for** 12 months prior to **and after** 3-Month Dosing Regimen denosumab administration for vertebral and nonvertebral fractures).

Descriptive statistics will be provided for other secondary endpoints (CHQ-PF-50 score, WBFPR scale and growth velocity).

The 6-Month Dosing Regimen safety analysis set will include all enrolled subjects who receive ≥ 1 dose of IP. The 3-Month Dosing Regimen safety analysis set will include all subjects in the full analysis set (FAS) who received ≥ 1 dose of IP under the 3-Month Dosing Regimen. The 3-Month Dosing Regimen safety analysis set and 6-Month Dosing Regimen safety analysis set will be used for the analysis of all safety endpoints. 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 IP and treatment-emergent adverse events of interest will also be provided. The incidence rate (number of events and exposure-adjusted rate) will be summarized. In addition, subject incidences of metaphyseal index Z-score above age-appropriate normal range, severe or symptomatic hypocalcemia, ONJ, abnormal molar eruption, abnormal mandibular shaping, and hypercalcemia will be summarized.

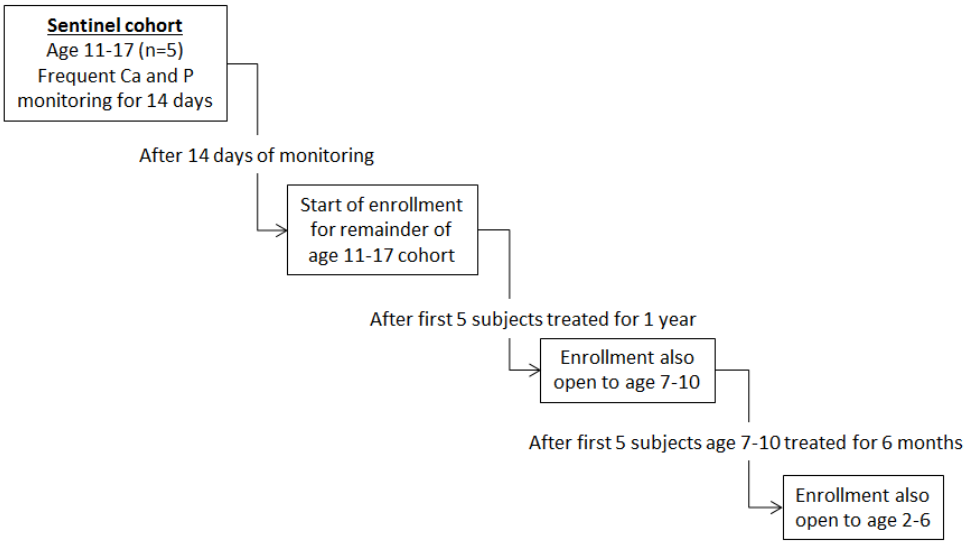
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen, Inc.

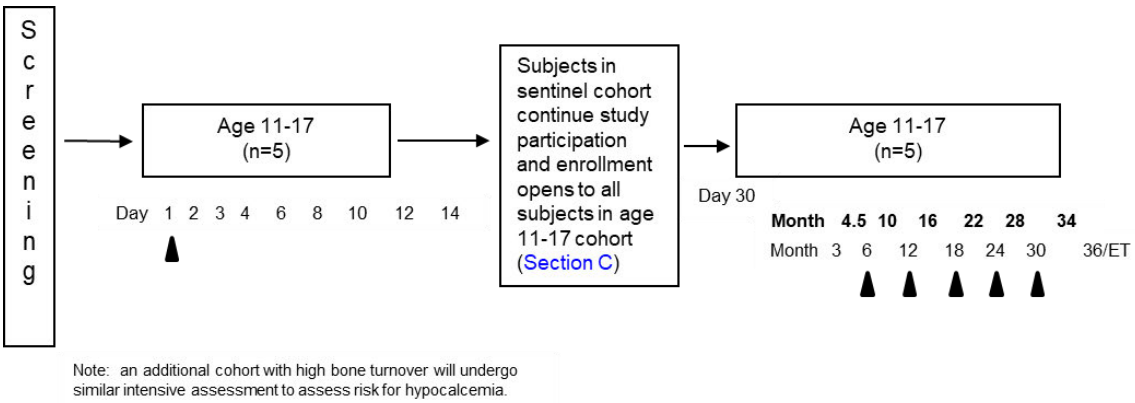
Data Element Standards Version(s)/Date(s):	Version 4.0 31 October 2013

Study Design and Treatment Schema for 6-Month Dosing Regimen

A. Gated cohort enrollment
(Refer also to sections B and C that are sub-schemas of Section A)

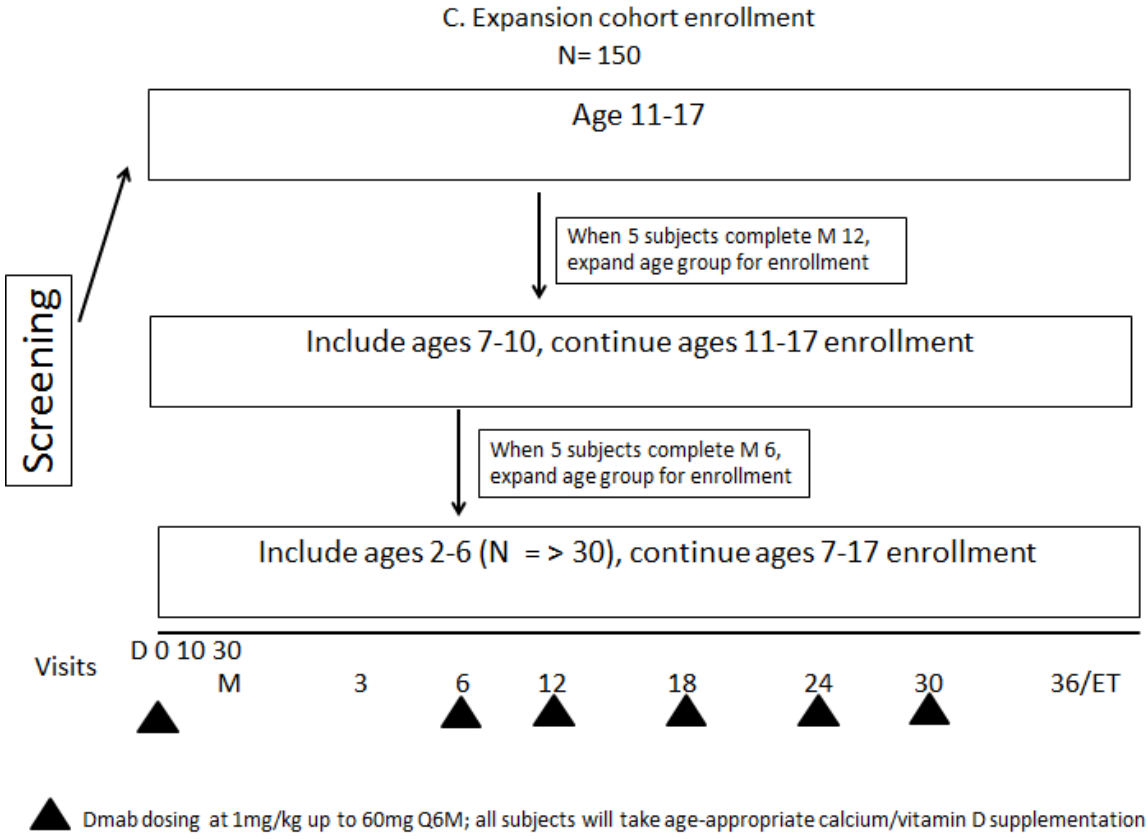


B. Sentinel Cohort
Mineral Homeostasis monitoring schedule

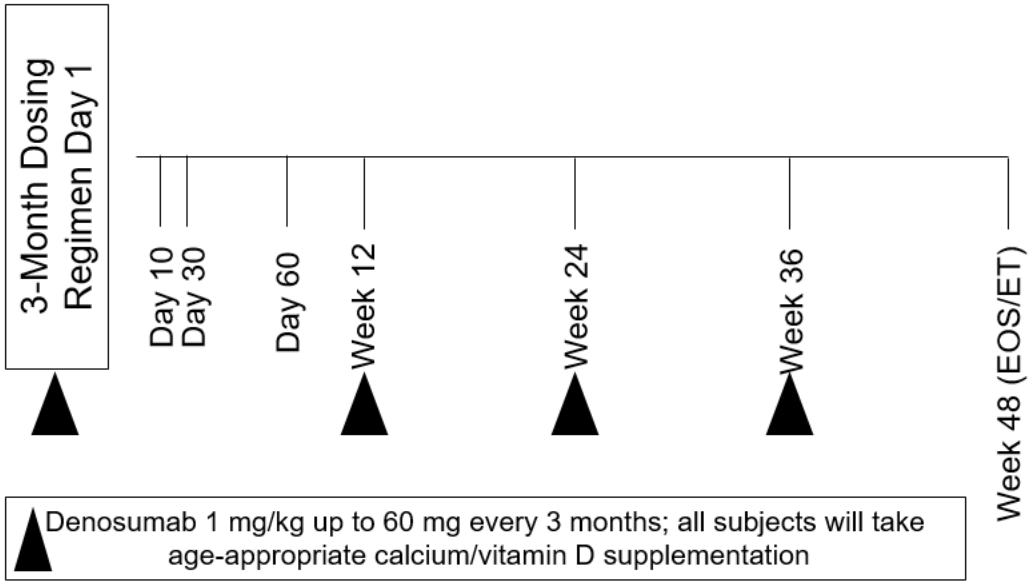


Note: an additional cohort with high bone turnover will undergo similar intensive assessment to assess risk for hypocalcemia.

▲ Dmab dosing at 1mg/kg up to 60 mg Q6M; all subjects will take age-appropriate calcium/vitamin D supplementation



Study Design and Treatment Schema for 3-Month Dosing Regimen



Study Glossary

Abbreviation or Term	Definition/Explanation
ACTH	adrenocorticotropic hormone
ADT	androgen deprivation therapy
AFF	atypical femoral fracture
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AP	anteroposterior
AST	aspartate aminotransferase
[redacted]	[redacted]
BMD	bone mineral density
BMI	body mass index
BSAP	bone-specific alkaline phosphatase
BTM	bone turnover markers
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CHAQ	Childhood Health Assessment Questionnaire
CHQ-PF-50	Child Health Questionnaire – Parent Form-50
CTCAE	Common Terminology Criteria for Adverse Events
COL1A1	collagen type I alpha 1 gene
COL1A2	collagen type I alpha 2 gene
CRF	case report form
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DXA	dual-energy X-ray absorptiometry
eCRF	electronic case report form
EDC	electronic data capture
EOS	**End of Study**
eGFR	estimated glomerular filtration rate
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
EMA	European Medicines Agency
End of Study (end of trial)	defined as the date when the last subject across all sites is last 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 Treatment (ET)	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject

Abbreviation or Term	Definition/Explanation
EU	European Union
FAS	full analysis set
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
Interactive Voice Response System (IVRS)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
Interactive Web Response System (IWRS)	web based technology that is linked to a central computer in real time as an interface to collect and process information.
IP	investigational product
IPIM	investigational product instruction manual
IRB	institutional review board
LLN	lower limit of normal
LS	least squares
IUD	intrauterine device
IUS	intrauterine hormonal releasing system
OI	osteogenesis imperfecta
ONJ	osteonecrosis of the jaw
PD	pharmacodynamic
PI	principal investigator
PTH	parathyroid hormone
PK	pharmacokinetic
PRO	patient-reported outcomes
SC	subcutaneous
sCTX	serum type I collagen C-telopeptide
SE	standard error
SFU	**safety follow-up**
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.

Abbreviation or Term	Definition/Explanation
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
ULN	upper limit of normal
US	United States
WBFPRS	Wong-Baker Faces Pain Rating Scale
3 Month Dosing day 1	Defined as the first date that protocol- specified investigational product(s)/protocol-required therapies at 3-Month Dosing Regimen is administered to the subject

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1. OBJECTIVES

1.1 Primary

To evaluate the effect of denosumab in lumbar spine bone mineral density (BMD) Z-score at 12 months, as assessed by dual-energy X-ray absorptiometry (DXA), in children 2 to 17 years of age (at the time of screening) on a 3-Month Dosing Regimen with osteogenesis imperfecta (OI).

1.2 Secondary

To evaluate denosumab in children 2 to 17 years of age (at the time of screening) with OI on a 3-Month Dosing Regimen with respect to:

- Change in lumbar spine BMD Z-score, as assessed by DXA, at 6 months
- Change in proximal femur BMD Z-score, as assessed by DXA, at 6 and 12 months (in subjects 5 years of age and older)
- Incidence of X-ray confirmed long bone and new and worsening vertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Incidence of X-ray confirmed new and worsening vertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Incidence of X-ray confirmed new vertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Incidence of X-ray confirmed improving vertebral fractures from **baseline of 3-**Month **Dosing Regimen** to 12 months on 3-Month Dosing Regimen
- Incidence of vertebral and nonvertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen (in subjects 5 years of age or older)
- Change in Child Health Questionnaire – Parent Form-50 (CHQ – PF-50) Physical Summary Score at 12 months
- Change in CHQ-PF-50 Psychological Summary Score at 12 months
- Change in Childhood Health Assessment Questionnaire (CHAQ) Disability Index Score at 12 months
- Change in Wong-Baker Faces Pain Rating Scale (WBFPRS) at 12 months
- Change in growth velocity (determined by calculating age-adjusted Z-scores for height, weight and body mass index [BMI]) at 12 months
- Serum denosumab concentration and bone turnover markers (BTM) collected **at 1,** 10, 30, and 60 days after the first dose of 3-Month Dosing Regimen and every 3 months in all subjects

1.3 Exploratory

[redacted]

[redacted]

1.4 Safety

To evaluate denosumab in children 2 to 17 years of age (at the time of screening) with OI on a 3-Month Dosing Regimen or 6-Month Dosing Regimen with respect to:

- Adverse events and serious adverse events
- Laboratory parameters
- Vital signs
- Antidenosumab antibodies
- Metaphyseal index
- Molar eruption and mandibular shaping
- Hypercalcemia

2. BACKGROUND AND RATIONALE

2.1 Disease

Osteogenesis imperfecta is a group of genetic skeletal disorders characterized by increased bone fragility, low bone mass (Rauch and Glorieux, 2004), and increased bone turnover (Rauch et al, 2009). Osteogenesis imperfecta is the most common form of primary osteoporosis in children with an estimated incidence of 1 per 25,000 live births (Byers, 2000).

At least twelve types of OI have been identified based on clinical phenotype and underlying genetic defect (Forlino and Marini, 2016; Marini and Blissett, 2013). The majority of individuals with OI are heterozygous for mutations in the type I collagen genes COL1A1 or COL1A2 that lead to quantitative and/or qualitative defects in collagen synthesis and negatively impact bone strength (van Dijk et al, 2012).

The clinical features of OI may include fractures, short stature, hyperlaxity of ligaments and skin, hearing loss, blue sclera, and dentinogenesis imperfecta (Marini et al 2017; Steiner et al, 2005). The clinical severity of OI caused by dominantly inherited collagen mutations varies from mild, non-deforming to perinatal lethal; most children with OI experience recurrent fractures, with or without progressive deformity, disability, and pain (Rauch and Glorieux, 2004).

The medical management of pediatric OI includes the orthopedic prevention and treatment of fractures, bowing, and scoliosis. Currently, there are no approved medicinal products for the treatment of OI, except for neridronate, which is only approved for the treatment of OI in Italy. Clinicians have been using bisphosphonates in

children with moderate to severe OI to reduce osteoclast activity and increase bone mass (even though abnormal collagen is usually present [Byers, 2000]) with the aim of reducing fractures (Rauch and Glorieux, 2004). Clinical trials of bisphosphonate treatment in pediatric OI have consistently shown increases in BMD, with variable effects on fracture reduction, bone pain**,** and quality of life (Castillo et al, 2009). Recent meta-analyses confirm the variable effect of bisphosphonates on fracture reduction (Dwan et al, 2016; Hald et al, 2015). Thus, an unmet need remains in children with OI.

Rationale for Dose Change

The change to 3-Monthly dosing stems from early findings that a significant number of subjects met BMD Z**-**score decline of more than 0.5 units. This decline was associated with a lower than anticipated increase in lumbar spine BMD from baseline in the whole population as compared to published studies on oral bisphosphonates. However, it should be noted that overall there was an upward trend. In addition, preliminary study data indicate that after administration of 1 mg/kg denosumab, pharmacokinetic (PK) exposures are cleared within 3 months and sCTx levels recover back to near baseline by 3 months. This is likely due to a faster rate of bone turnover in the pediatric OI population (Rauch et al, 2000; Baron et al, 1983) and to higher RANKL target expression in subjects with pediatric OI compared to normal children (Brunetti et al, 2016). These data support that adjustment of the dose regimen from 6-Month Dosing Regimen to 3-Month Dosing Regimen is appropriate for evaluation in pediatric OI subjects.

2.2 Amgen Investigational Product Background

Denosumab is a fully human monoclonal antibody that binds with high affinity (dissociation equilibrium constant [K_d] 3 x 10^{-12} M) and specificity to RANKL and neutralizes the activity of RANKL, preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian Chinese hamster ovary cells. It consists of 2 heavy chains of the immunoglobulin (Ig)G2 subclass and 2 light chains of the kappa subclass. The heavy and light chains are covalently linked through disulfide bonds.

Denosumab, by inhibiting RANK ligand, has the potential to treat diseases characterized by increased osteoclast-mediated bone loss and increased fracture risk. In children with OI, denosumab may have benefit due to its unique mechanism of action, reversible PK, and ease of administration. In a mouse model of moderate to severe OI, both RANKL

inhibition (via RANK-Fc) and alendronate significantly reduced fracture incidence when treatment was started in neonatal animals (Bargman et al, 2012).

Denosumab is currently indicated for: treatment of postmenopausal women with osteoporosis; treatment of men with osteoporosis; treatment of bone loss in men receiving androgen deprivation therapy (ADT) for prostate cancer, treatment of bone loss in women receiving aromatase inhibitor therapy for breast cancer, and treatment of adult glucocorticoid-induced osteoporosis. Additional information is provided in the Denosumab Investigator's Brochure.

2.3 Pediatric Risk Assessment

Although denosumab has been studied in an adolescent population in the oncology setting of Giant Cell Tumor of Bone, it has not been studied in the setting of skeletal fragility in children. Several aspects will be investigated and are further considered in Section 7. Volumes of blood withdrawn for analysis in association with clinical monitoring will be minimized as appropriate for this pediatric population based on body weight (EU Ethical Considerations, 2008).

Preliminary study data indicate that after administration of 1 mg/kg denosumab, PK exposures are cleared within 3 months and sCTx levels recover back to near baseline by 3 months. This is likely due to higher RANKL target expression levels and a faster rate of bone turnover in the pediatric OI population (Brunetti et al, 2016; Rauch et al, 2000; Baron et al, 1983).

Recently, life threatening events of hypercalcemia were reported on denosumab 1 mg/kg Q3M regimen in the pediatric OI subjects within this study. Amgen considers that the overall benefit:risk profile of Prolia (denosumab) (Q3M/Q6M) is not favorable in the OI pediatric patient population based on the data observed.

2.3.1 Pharmacokinetics/Pharmacodynamics (BTM)

Pharmacokinetic/PD analysis will be performed on all subjects on 3-Month Dosing Regimen to further evaluate the impact of 3-Month Dosing in this pediatric population with OI to add to the data obtained during the trial during the 6-Month Dosing Regimen.

2.3.2 Safety

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 ADT for prostate cancer (Study 20040138) or aromatase inhibitor therapy for breast cancer

(Study 20040135); and men with osteoporosis (Study 20080098) and glucocorticoid-induced osteoporosis (Study 20101217). In addition, denosumab also 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 in adults 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 reported in every study evaluated to date. 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 (ONJ), atypical femoral fracture ([AFF] reported rarely in patients treated with denosumab and not evaluable in subjects with OI); eczema (including dermatitis, allergic dermatitis, atopic dermatitis, and contact dermatitis), pain in the extremity**,** musculoskeletal pain, and multiple vertebral fractures following discontinuation of denosumab treatment. Additionally, hypercalcemia following denosumab discontinuation is an important potential risk in patients with growing skeletons. There may be a possibility hypercalcemia can occur at the end of the dosing interval when a subject is still receiving investigational product (IP).

As of 20 April 2020 with the every 6 months dosing regimen in Study 20130173, 153 subjects had received IP.

As of 03 August 2021, 60 subjects had received at least 1 dose of Prolia at the 1 mg/kg Q3M dosing regimen.

Of the 153 subjects who had received IP, 149 (97.4%) had at least 1 treatment-emergent adverse event; 121 (79.1%) subjects, 57 (37.3%) subjects, and 1 (0.7%) subjects had grade 2, 3, and 4 adverse events, respectively. A total of 47 (30.7%) subjects had a serious adverse event, and 5 (3.3%) subjects had an adverse event leading to withdrawal of IP. There were no fatal adverse events**.**

In the Q6M dosing regimen, hypercalcemia events including events of calcium ionized increased and blood calcium increased have been reported in 24 (15.7%) study subjects. No serious adverse events of hypercalcemia have been reported. The majority of hypercalcemia adverse events were grade 1 in severity. Three subjects had events grade 2 in severity including the following verbatim events: asymptomatic

increased level of ionized calcium reported on day 29; calcium blood increased - nonsymptomatic, underlying diagnosis unknown on day 30; and a report of hypercalcemia (no clinical consequences) beginning as a grade 1 hypercalcemia 12 days following the previous dose. The severity grade was increased to 2 on day 85 and the event resolved on day 180 following the previous dose.

Twelve subjects reported events of hypercalcemia ≤ 30 days from the most recent dose. Six subjects reported events 31 to 90 days following the most recent dose. Five subjects reported events > 90 days to 180 days following the most recent dose. One subject reported hypercalcemia > 180 days (day 196) following the most recent dose. Overall, the events of hypercalcemia reported to date have not been clinically significant. The majority of the events resolved and no action was taken with IP.

In the combined Q3M/Q6M dosing cohorts, treatment-emergent adverse events of hypocalcemia have been reported in **19** (**12.4**%) of study subjects. There have been no **cases of positively adjudicated osteonecrosis of the jaw**.

In a substudy assessment of urine calcium, deoxypyridinoline/creatinine (DPD/creat) ratio, and urine N-telopeptide (NTX) for each treatment cycle shows the following trends:

- Urine calcium/creatinine ratio declines in first 2 weeks following IP administration and increases to slightly above baseline in weeks 12-18
- Absolute value and DPD/ creatinine ratio decreases within the first 2 weeks following dosing and subsequently increases by week 8 and returns to or slightly above baseline between 12-18 weeks following IP administration
- Urine NTX similarly decreases within first 2 weeks, increasing by week 8 and is back to baseline levels by 18 weeks

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.

2.3.2.1 Hypocalcemia

Skeletal turnover rates vary by age and are higher in children than adults. These higher bone turnover rates expected at baseline in children with OI 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 other than OI (eg, fibrous dysplasia and juvenile Paget's disease) have described disturbances in mineral

metabolism, including hypocalcemia and hypophosphatemia (Boyce et al, 2012; Grasemann et al, 2013).

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

- calcium and vitamin D supplementation will be given and serum calcium and phosphorus concentrations will be monitored throughout the study on a regular basis.
- at all study visits, signs and symptoms of hypocalcemia will be assessed and subjects reminded of importance of taking calcium and vitamin D.
- occurrence of severe or symptomatic hypocalcemia will prompt discontinuation of study medication and institution of appropriate medical treatment.
- enrollment in the study will be gated by age group, as described in Section 3.1.1.
- mineral homeostasis will be monitored more frequently over 14 days after administration of the first dose of denosumab in a sentinel cohort comprised of first 5 subjects enrolled in the 11-17 year age group to permit adaptation of subsequent mineral homeostasis assessments for all study subjects, as appropriate. A similar approach will be employed in the first 5 subjects of any age who have increased bone turnover defined as meeting 2 of the 3 following criteria: (1) untreated with bisphosphonates for 4 years prior to entry in the trial; (2) Type 3 OI with the following characteristics: height $< 3^{rd}$ percentile and bowed extremities (or saber shins); or (3) Tanner stage 3 or 4.
- subjects will not be eligible to participate who have evidence of hypocalcemia or diseases that increase the risk of hypocalcemia, including, but not limited to, malabsorption and kidney disease, as well as subjects with additional risk factors for detrimental effects of hypocalcemia, eg, a history of long QT syndrome.

2.3.2.2 Hypercalcemia

As of 7 September 2021, a total of 56 events of hypercalcemia were reported in the pediatric studies 20130173 and 20170534. Of these 56 events, 5 events of severe hypercalcemia grade 4 (n = 2) and grade 3 (n = 3) were reported in study 20130173. The remaining 51 hypercalcemia events were of grade 1 (n = 47) and grade 2 (n = 4).

Thirteen events, including 5 events of severe hypercalcemia (≥ grade 3) occurred in subjects receiving Q3M dosing in studies 20130173 (n = 12) and 20170534 (n = 1). These events occurred in 12 subjects between age of 5 years and 13 years. Three events were serious and the remaining 10 events were non serious. Nine (69%) of these events occurred after the subjects had received 3 or 4 doses of denosumab. Twelve events occurred toward the end of dosing regimen between 60 and 99 days after the prior dose. The 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. Two subjects had hypercalcemia grade 4 and both required hospitalization and are described below.

- **In one 13-year-old male subject, the grade 4 event occurred 77 days after the most recent dose and was life threatening. He was treated with intravenous normal saline. The event resolved.**
- **In one 7-year old male subject, the grade 4 event occurred 91 days after the most recent dose. The subject presented with severe dehydration, reduced glomerular filtration rate (GFR) and seizures resulting in sedation, intubation and assisted ventilation. Rescue medication (IV Zoledronic Acid) was required to stabilize the subject.**

There were 43 events reported in 31 subjects receiving Q6M dosing in the studies 20130173 (n = 41) and 20170534 (n = 2). These events occurred in subjects between the ages of 2 and 16 years. There were 40 events of grade 1 hypercalcemia and 3 events of grade 2 hypercalcemia.

The higher bone turnover rates expected at baseline in children with OI **appears to** increase the risk for rebound hypercalcemia in the latter part of the dosing interval due to **a rapid** release of bone turnover **marker** inhibition. In addition, recent clinical reports of denosumab administration in pediatric patients with disorders of high bone turnover other than OI (eg, fibrous dysplasia and juvenile Paget's disease) have described the occurrence of rebound hypercalcemia (Boyce et al, 2012; Grasemann et al, 2013)**.**

Based on the benefit:risk profile of denosumab in pediatric OI study, Amgen made the decision to stop further dosing of denosumab in this study and subjects will be followed for safety for 24 weeks from the last dose of denosumab.

2.3.2.3 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 modeled 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 ≥ 2 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 minimizes 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 on 3-Month Dosing Regimen throughout the study in subjects with open growth plates who do not have bilateral hardware only, as only in subjects with open growth plates who do not have bilateral hardware 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 consistent with local institutional guidelines, will prompt discontinuation of study medication and institution of appropriate follow-up.

2.3.2.4 Tooth Eruption

RANKL plays an important role in tooth eruption. In nonclinical studies conducted in neonatal rats, OPG-Fc and alendronate administration impaired the eruption of 2nd and 3rd molars and also reduced incisor growth. These findings were at least partially reversible within 10 weeks of discontinuing OPG-Fc. 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.

2.3.2.5 Osteonecrosis of the Jaw (ONJ)

Cases of ONJ have been reported in association with antiresorptive use. ONJ may be associated with pain and/or infection of the jaw bone, teeth or gums resulting in a non-healing area of exposed bone in the mouth. How this happens is poorly understood. One hypothesized mechanism involves interference with bone remodeling as a result of decreased osteoclast activity. In this study, all events reported as ONJ, or

those coded to prespecified terms potentially indicative of ONJ, will be reviewed by an independent adjudication committee.

To minimize this risk, the following strategies will be employed: Potential infection of jaw bone, tooth, or gum infections will be monitored with oral visual inspection as part of the scheduled physical examinations (including after molar eruption) and X-ray assessments when indicated.

2.3.2.6 Atypical Femoral Fracture

Cases of AFF have been reported in patients with osteoporosis in association with antiresorptive use. Some case series have reported a possible association between AFF and long-term alendronate therapy (Odvina et al, 2010; Lenart et al, 2009; Odvina et al, 2005), while others have not (Abrahamsen et al, 2009). Osteogenesis imperfecta is characterized by increased bone fragility and resulting frequent fractures that are often precipitated by minimal trauma. The most frequent fracture site in patients with OI includes the femur (Folkestad et al, 2017). The major defining features of AFF include a fracture that is associated with minimal or no trauma, a subtrochanteric or femoral shaft location, and a fracture line that is transverse in orientation. This definition however, does not apply to pathological fractures associated with primary or metastatic bone tumors and certain bone diseases (eg, Paget's disease, fibrous dysplasia) (Shane et al, 2014). The increased rate of femoral fractures in OI is likely related to the brittleness of bones and the femoral fractures in OI tend to resemble AFF. Earlier data suggested an increased risk of AFF-like femur with antiresorptive (bisphosphonate) use (Nicola**o**u et al, 2012), but more recent studies suggest that the atypical features of femur fractures were likely related to severity of OI and not bisphosphonate use (Trejo et al, 2017; Vuorimies et al, 2017).

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

- Subjects will be seen no less frequently than every 3 months and can have hip X-rays where clinically suspected. All femur fractures will be reviewed by the study team and site investigator to determine if change in treatment is required.

In alignment with the Study 20130173 Data Monitoring Committee (DMC) terminology, all femur fractures will be reviewed as typical OI femur fractures (TOIFF).

2.4 Rationale

This study is part of a Pediatric Investigation Plan for denosumab (Prolia®) that was agreed upon with the European Medicines Agency (EMA). The purpose of this study is to evaluate the efficacy, safety, and PK of denosumab (1 mg/kg, up to a maximum of

60 mg, administered subcutaneously once every 3 months) in children with OI. Change from baseline of 3-Month Dosing Regimen in lumbar spine BMD, as assessed by Z-score, will be calculated and compared to age- and sex-comparable historical data from 3 published, randomized, controlled trials in pediatric subjects with OI and to the 3-Month Dosing Regimen baseline.

The 3-Month primary endpoint is based on comparison with 3-Month baseline which is at the end of 6 month dosing. Including subjects with 6 month exposure prior to 3 Month dosing will likely attenuate the effect size to be observed for the 3-Month primary endpoint. Thus this is a more conservative approach to show statistical significance. In addition, the 6 Month exposure will be used as a covariate to account for its effect on 3 Month primary endpoint.

The subject incidence of fractures also will be summarized **for** 6-Month **and 3-month** Dosing Regimen. It is expected that the change in lumbar spine BMD Z-score following 12 months of denosumab treatment using 3-Month Dosing Regimen will be greater than historical controls. Safety of subjects during study conduct will be monitored by the study team and a DMC. 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.

Rationale for Stopping Denosumab Administration

The independent DMC convened on 24 September 2021 to review efficacy and safety data on Study 20130173. After reviewing the data, the DMC determined that the benefit observed with Q3M dosing in the OI study does not outweigh the potentially life-threatening events of the observed severe hypercalcemia events (Section 2.3.2.2).

As of 30 September 2021, due to the life-threatening risk of hypercalcemia, subjects on study who had not completed their EOS visit were immediately discontinued from IP, and will be followed for safety for 24 weeks following the last dose of IP per the updated Schedule of Assessments (Table 7-5). The last dose of IP will be considered week 0. Subjects who have been on alternative therapy for more than 6 months or whose last dose of IP was greater than 24 weeks, no additional 24-week safety follow-up is required. These subjects can follow the previous protocol (protocol amendment 6) and complete the EOS CRF. Subjects whose last dose was between 12 and 24 weeks ago can complete the

EOS assessments at week 24 per the updated Schedule of Assessments (Table 7-5).

2.5 Clinical Hypotheses

The hypothesis of the study is that the change from baseline in lumbar spine BMD Z-score following 12 months of denosumab treatment with 3-Month Dosing Regimen in children 2 to 17 years of age (at the time of screening) with OI will be greater than that from historical controls (ie, placebo or untreated subjects) (Letocha et al, 2005; Rauch et al, 2009; Ward et al, 2011) which was estimated to be 0.01 (95% CI: -0.17, 0.18).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a single-arm, multicenter, phase 3 study to demonstrate the superiority of denosumab administration compared with historical controls as measured by change from baseline in lumbar spine BMD Z-score at 12 months and to evaluate the safety, efficacy, and PK in children with OI. The effect of denosumab administered every 3 months will be evaluated based on comparison in BMD Z-score change from baseline of 3-Month Dosing Regimen to 12 months with historical controls derived from published randomized, controlled trials (Letocha et al, 2005; Rauch et al, 2009; Ward et al, 2011).

BMD, fracture, growth velocity, and other efficacy and safety data also will be collected. Questionnaires will be administered to subjects and their parents to evaluate patient-reported outcomes (PROs). Blood samples will be collected to measure serum blood levels of denosumab. For a female who has a Tanner stage 2 or greater, or has had menarche, a urine pregnancy test will be performed prior to IP administration at every visit and End of Study (EOS).

Radiographic assessments will be performed to monitor skeletal impact of denosumab treatment during the 3-Month Dosing Regimen, including: metaphyseal modeling, mandibular shape, and unerupted molars. Treatment with denosumab will be stopped for subjects in the following situations:

- decline in BMD Z-score by at least 0.5 units at any 6-month assessment compared to the 3-Month Dosing Regimen baseline
- 4 or more new long bone and/or vertebral fractures in any 6-month period (additional spine X-rays should be obtained if clinically indicated)
- 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 consistent with local institutional guidelines
- severe or symptomatic hypocalcemia

- severe or symptomatic hypercalcemia, which requires the use of a rescue medication for management
- ONJ
- dental abnormalities requiring invasive dental procedures, as determined by investigator and/or treating dentist and within the local institutional practice guidelines
    - Denosumab administration should be withheld 30 days prior to an invasive dental procedure and until complete mucosal healing is observed and documented (refer to Section 6.2.3 for guidance on restarting IP)
- pregnancy
- Potential events of ONJ will be adjudicated by an independent adjudication committee using pre-defined criteria. 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 all data in order to monitor safety results to protect subjects. To minimize the potential introduction of bias, the DMC members will not have any direct contact with the site personnel, or subjects.

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

The study endpoints are defined in Section 10.1.1.

3.1.1 6-Month Dosing Regimen

Approximately 150 subjects between 2 to 17 years of age will be enrolled, including at least 30 subjects younger than 7 years of age (at time of initial enrollment). All subjects will receive denosumab 1 mg/kg (up to a maximum of 60 mg) subcutaneously every 6 months for 36 months, and all subjects will receive age appropriate calcium and vitamin D (Study Design and Treatment Schema are provided at end of protocol synopsis section). Subjects meeting eligibility criteria will be enrolled in the study to receive treatment with denosumab. Although enrollment in the study will not be stratified, it will be gated as follows:

- Older children (11 to 17 years of age) will be enrolled first because they will be the most skeletally mature and are more verbal and cognizant to describe adverse events.
- The first 5 subjects enrolled in the 11 to 17 years-of-age cohort (sentinel cohort) will undergo intensive mineral homeostasis monitoring for the first 14 days after administration of IP, to permit adaptation of subsequent mineral homeostasis assessments for all study subjects, as appropriate. Once these 5 subjects have completed 14 days of mineral homeostasis monitoring, enrollment will be open to the remainder of the 11 to 17 years-of-age cohort.
- When the first 5 subjects in the 11 to 17 years-of-age cohort have been treated for 12 months, enrollment will be open to the next age group (7 to 10 years of age).

- Enrollment will be open to children 2 to 6 years of age after the first 5 subjects between 7 to 10 years of age have been treated for 6 months.

At least 30 subjects younger than 7 years of age (at time of initial enrollment) will be enrolled.

Calcium and vitamin D supplementation will be given to all study subjects and serum calcium and phosphorus concentrations will be monitored throughout the study on a regular basis. Mineral homeostasis will be monitored more frequently over 14 days after administration of the first dose of denosumab in a sentinel cohort comprised of the first 5 subjects enrolled in the 11 to 17 years-of-age group to permit adaptation of subsequent mineral homeostasis assessments for all study subjects, as appropriate. A similar approach will be employed in the first 5 subjects of any age who have increased bone turnover, defined as meeting 2 of the 3 following criteria: (1) untreated with bisphosphonates for 4 years prior to entry in the trial; (2) Type 3 OI with the following characteristics: height < 3rd percentile and bowed extremities (or saber shins); or (3) Tanner stage 3 or 4. The first 5 subjects meeting the criteria for increased bone turnover must undergo frequent mineral homeostasis monitoring for the first 14 days after denosumab administration according to the above schedule. If a subject within the first 5 meeting the criteria for increased bone turnover is not willing to comply with these requirements, then he/she cannot be enrolled until the first 5 subjects have completed these required assessments and the regular monitoring schedule can be safely implemented.

3.1.2 3-Month Dosing Regimen

Sixty previously enrolled subjects were transitioned to a 3-Month Dosing Regimen**, among them, approximately 20 subjects were younger than 7 years of age (at time of initial enrollment). Based on the life-threatening events of hypercalcemia observed, Amgen evaluated that benefit:risk profile of denosumab is not favorable. Per DMC recommendation and Amgen decision, an urgent safety measure was issued to stop IP with the EOS visit 24 weeks after the last dose of IP. See Section 3.5.2.**

3.2 Number of Sites

Approximately 40 sites in North America, Europe, and Australia may participate in this study.

3.3 Number of Subjects

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

Approximately 150 subjects 2 to 17 years of age will participate in the study of which at least 30 subjects will be less than 7 years of age (at time of initial enrollment).

Sixty subjects transition**ed** to the 3-Month Dosing Regimen. Those subjects who do not consent to the **24-week safety follow up** will end the study.

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

Each subject duration may vary between 36 to **51** months. The maximum duration of trial for each subject **could** be **51** months **(84 weeks)**.

3.5.2 End of Study

An individual subject is considered to have completed the study if he/she has completed at least 12 months of 3-Month Dosing Regimen and a minimum of 36 months on study. **As of 30 September 2021, due to the life-threatening risk of hypercalcemia, subjects on study who had not completed their EOS visit were immediately discontinued from IP, and will be followed for safety for 24 weeks following the last dose of IP per the updated Schedule of Assessments (Table 7-5). Subjects who have been on alternative therapy for more than 6 months or whose last dose of IP was greater than 24 weeks, no additional 24-week safety follow-up is required. These subjects can follow the previous protocol (protocol amendment 6) and complete the EOS CRF. Subjects whose last dose was between 12 and 24 weeks ago can complete the EOS assessments at week 24 per the updated Schedule of Assessments (Table 7-5).**

End of Study (End of Trial): the end of the study/trial is defined as the date when the last subject across all sites is last 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).

Before any study-specific activities/procedures related to this amendment, and in addition to the appropriate written informed consent from a legally acceptable

representative, the assent of the child also must be obtained, as appropriate to the age of the subject and/or based on local regulations where approved (see Section 11.1). Subjects who remain on study (have not previously completed Month 36/EOS on 6-Month Dosing Regimen) will be reconsented at their next visit, and transition to a 3-Month Dosing Regimen. Subject eligibility will not be re-assessed at time of transition to 3-Month Dosing Regimen. Refer to Section 7.1 for Schedule of Assessments at time of dose transition. Subjects who do not reconsent to a 3-Month Dosing Regimen will be discontinued from IP as withdrawn consent and withdrawn from this study. Subjects who do not reconsent will be given the opportunity to transition to Study 20170534.

4.1 Inclusion and Exclusion Criteria

Eligibility criteria relates to initial enrollment into this study. Subjects reconsenting to a 3-Month Dosing Regimen will not repeat eligibility assessments; however, any subjects who previously ended IP who are receiving alternative therapies must discontinue these before resuming treatment with denosumab.

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 written assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated

102. Children 2 to 17 years of age inclusive at screening

103. Clinical diagnosis of OI defined as a clinical history consistent with type I-IV OI as determined by presence of expected phenotype (examples include: facial shape, voice, blue sclera, dentinogenesis imperfecta, typical radiographic features, fracture pattern) and lack of additional features unrelated to type I-IV OI (eg, blindness; mental retardation, neuropathy, craniosynostosis; premature exfoliation of normal appearing deciduous teeth)
    - If familial, also must be autosomal dominant

104. Clinical severity of OI as defined by
    - 2 or more prevalent vertebral compression fractures; OR
    - 1 prevalent vertebral compression fracture and 1 or more nonvertebral fractures within the previous 2 years; OR
    - 3 or more fractures within the previous 2 years

4.1.2 Exclusion Criteria

Subjects meeting any of the following criteria at screening are not eligible for enrollment:

201. Inability or unwillingness to comply with the requirements for frequent calcium and phosphorus monitoring for 14 days after the first dose of denosumab (only applies to the first 5 subjects 11 to 17 years of age enrolled in the study and the

first 5 subjects of any age meeting the criteria for increased bone turnover (see Section 2.3.2.1)

202. Currently unhealed fracture or osteotomy, as defined by orthopedic opinion
203. Osteotomy within 5 months prior to screening
204. Evidence of untreated oral cavities or oral infections
205. Recent or planned invasive dental procedure
206. Surgical tooth extraction which has not healed by screening
207. History of an electrophoresis pattern inconsistent with type I to IV OI
208. History of known mutation in a gene other than COL1A1/COL1A2 causing OI or other metabolic bone disease

Abnormalities of the following per central laboratory reference ranges at screening

209. Serum albumin-corrected calcium < lower limit of normal (LLN)
210. Serum vitamin D < 20 ng/mL; rescreening for vitamin D level < 20 ng/mL will be allowed, after adequate supplementation
211. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) > 1.5 x upper limit of normal (ULN)
212. Total bilirubin (TBL) > 1.5 x ULN (subjects with Gilbert syndrome are eligible)
213. Serum phosphorus < LLN
214. Serum alkaline phosphatase > 20% above the ULN or > 20% below the LLN
215. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (calculated by the Schwartz equation at screening)

Evidence of any of the following:

216. Current hyperthyroidism (unless well-controlled on stable antithyroid therapy)
217. Current clinical hypothyroidism (unless well-controlled on stable thyroid replacement therapy)
218. History of hyperparathyroidism
219. Current hypoparathyroidism
220. Current, uncontrolled hypercalcemia (albumin-corrected serum Ca > 10% ULN)
222. History of osteomalacia or rickets (chart review)
223. Other bone diseases that affect bone metabolism (eg, osteoporosis pseudoglioma syndrome, idiopathic juvenile osteoporosis, osteopetrosis, hypophosphatasia) (chart review)
224. History of autoimmune disease
225. History of malabsorption (in children with serum albumin < LLN, malabsorption should be clinically ruled out by the investigator to confirm eligibility)

226. History of rare hereditary problems of fructose intolerance
227. History of long QT syndrome
228. History of non-healing osteotomy
229. History of malignancy
230. History of alcohol or drug abuse
231. History of any solid organ or bone marrow transplant
232. Contraindicated or poorly tolerant of denosumab therapy
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. Currently pregnant or planning a pregnancy during the study and for an additional 5 months after the last dose of IP (denosumab)
236. Currently breastfeeding or planning on breastfeeding during the study and for an additional 5 months after the last dose of IP (denosumab)
237. 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 IP (denosumab) (See Section 6.8.1)

Received other osteoporosis treatment or bone active treatment with the following guidelines:

238. Prior treatment with
    - denosumab
    - fluoride or strontium for bone disease (fluoride taken for routine dental care is permitted)
    - parathyroid hormone (PTH) or PTH derivatives within 12 months prior to screening
    - zoledronic acid within 6 months prior to screening
    - oral bisphosphonates or intravenous bisphosphonates other than zoledronic acid, if the first dose of denosumab would be before their next scheduled bisphosphonate dose would have been given
239. Administration of systemic glucocorticoids (≥ 5.0 mg prednisone equivalents/day for more than 10 days) within 3 months prior to screening. Topical and inhaled glucocorticoids will be allowed.
240. Administration of any of the following treatment within 3 months prior to screening:
    - Growth hormone (subjects on stable dose of growth hormone for at least 3 months prior to screening will be allowed)
    - Calcitonin
    - Cathepsin K inhibitor

- Other bone active drugs including anti-convulsants (except gabapentin and benzodiazepines) and heparin
- Chronic systemic ketoconazole, androgens, adrenocorticotropic hormone (ACTH), cinacalcet, aluminum, lithium, protease inhibitors, gonadotropin-releasing hormone agonists

241. Received immunosuppressant therapy other than glucocorticoids

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

243. Symptoms associated with skull abnormalities such as basilar invagination, basilar impression or Chiari malformation (eg, headache induced by coughing or straining for stool, or parasthesias or weakness)

244. Rodding surgery within 5 months prior to screening or not yet healed per orthopedic surgeon

245. Spinal fusion surgery within 5 months prior to screening or not yet healed per orthopedic surgeon

246. Inability to consume milk

247. Planned orthopedic surgery that, in the opinion of the principal investigator (PI), would require missing any dose of denosumab in year 1 or 2 or more doses thereafter

248. Currently receiving treatment in another investigational drug study, or less than 30 days since ending treatment on another investigational drug study(s), or current or planned participation in a clinical trial that would preclude compliance with study requirements

249. Other investigational procedures while participating in this study are excluded

250. Known intolerance to calcium or vitamin D supplements

251. 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's safety or interfere with the study evaluation, procedures or completion

252. Subject will not be available for protocol-required study visits, to the best of the subject and investigator's knowledge

253. 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

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (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.

5.1 Enrollment into 6-Month Dosing Regimen

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 Interactive Voice Response System/Interactive Web Response System (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 enrollment number assigned for the study.

Enrollment/Treatment Assignment

After completing all screening procedures and meeting all eligibility criteria, subjects will be enrolled in the study to receive a subcutaneous (SC) injection of denosumab. Enrollment will be gated as follows:

- Older children (11 to 17 years of age) will be enrolled first because they will be the most skeletally mature and are more verbal and cognizant to describe adverse events.
- The first 5 subjects enrolled in the 11 to 17 years-of-age cohort (sentinel cohort) will undergo intensive mineral homeostasis monitoring for the first 14 days after administration of IP, to permit adaptation of subsequent mineral homeostasis assessments for all study subjects, as appropriate. Once these 5 subjects have completed 14 days of mineral homeostasis monitoring, enrollment will be open to the remainder of the 11 to 17 years-of-age cohort.
- When the first 5 subjects in this age group have been treated for 12 months, enrollment will be open to the next age group (7 to 10 years of age).
- Enrollment will be open to children 2 to 6 years of age after the first 5 subjects between 7 to 10 years of age have been treated for 6 months.

At least 30 subjects younger than 7 years of age (at time of initial enrollment) will be enrolled.

A subject will be considered enrolled once he/she meets eligibility criteria and an enrollment call is placed in IVRS/IWRS. It is therefore very important to place the enrollment call only after the subject's eligibility and willingness to participate has been confirmed, as the subject cannot be 'unenrolled'.

The IVRS/IWRS will be utilized to complete the enrollment of each subject that is ready to be enrolled. Specific details regarding enrollment and treatment assignment procedures will be provided separately by the IVRS vendor.

5.2 Transition to 3-Month Dosing Regimen

Due to the life-threatening risk of hypercalcemia, an urgent safety measure has been implemented to stop all treatment with IP with the EOS visit 24 weeks after the last dose of IP. See Section 3.1.2.

Before subjects can transition to a 3-Month Dosing Regimen, Amgen requires a copy of the site's written IRB/IEC approval of the protocol amendment and re-consent form. All legally acceptable representatives must personally sign and date the re-consent form and subjects should sign the subject assent form as applicable by local law before commencement of 3-Month Dosing Regimen/procedures.

A subject call will be placed in the IVRS/IWRS at time of re-consent and transition to the 3-Month Dosing Regimen. The investigator is to document this decision, and date of dosing schedule change, in the subject's medical record.

All subjects who remain on study (have not previously completed Month 36/EOS under the 6-Month Dosing Regimen) will be eligible to transition to the 3-Month Dosing Regimen, unless they ended treatment due to an adverse event. Subjects may be consented and transition to the 3-Month Dosing Regimen up to and including the date they attend for a Month 36 visit under the 6-Month Dosing Regimen.

Should a subject decide not to re-consent, subject will discontinue IP and study. See Section 8.3 for additional guidance.

6. TREATMENT PROCEDURES

Denosumab administered at a dose of 1 mg/kg (up to a maximum of 60 mg) is considered to be an IP in this study. A manual containing detailed information regarding the storage, preparation and administration of IP and brief information about other

protocol-required drugs will be provided separately in the **modular** Investigational Product Instruction Manual (IPIM).

6.1 Classification of Product(s) and/or Medical Device(s)

The Amgen IP used in this study includes denosumab.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-Amgen non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

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

6.2 Investigational Product

6.2.1 Amgen Investigational Product Denosumab

Denosumab 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. All subjects will receive a SC injection of denosumab every 6 months during the 6-Month Dosing Regimen. Subjects who transition to the 3-Month Dosing Regimen will receive an injection of denosumab every 3 months. All SC injections must be administered by authorized site personnel. The denosumab SC injection should be administered as the last procedure after all other study visit procedures have been completed. The injection should not be administered in the same arm from which blood is drawn.

6.2.2 Dosage, Administration, and Schedule

Each site will be supplied with denosumab such that each box will contain 1 vial of 70 mg/mL denosumab. There is no experience of overdosage with denosumab.

The site personnel will call IVRS/IWRS to obtain the appropriate box numbers at each scheduled dosing visit. The call to enroll the subject and to receive the day 1 injection should only be made after the subject has been determined to be eligible for the study. Denosumab will be administered at a dose of 1 mg/kg body weight, but the total dose must not exceed 60 mg per subject at any visit. Please refer to specific instructions provided by the IVRS/IWRS vendor for additional information.

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

Denosumab will be administered as a weight-based dose determined based on each subject's weight assessed at the time of dosing. There are no additional dose adjustments for the SC IP.

Blood draws and safety assessments on day 1 of the 3-Month Dosing Regimen should be performed before denosumab administration. 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.

Serum calcium and phosphorus concentrations will be closely monitored during the study.

Dosing may be delayed if a subject has bone surgery scheduled. Dosing with denosumab can be continued after the surgery at the investigator's discretion.

6.2.3.1 6-Month Dosing Regimen

In order to better evaluate and characterize the risk for hypocalcemia and hypophosphatemia, more frequent monitoring of mineral homeostasis after the first dose of denosumab for 14 days will be implemented in the first 5 subjects enrolled in the study. Serum calcium and phosphorus concentrations will be checked daily at the local and central laboratories for the first 3 days after administration of the first dose of denosumab and every other day thereafter for a total of 14 days in this 5-subject sentinel cohort.

If no concerns arise from dosing of the sentinel cohort over 14 days after the first administration of denosumab that warrant adaptation of the mineral homeostasis assessment schedule, enrollment will be opened for the remainder of the subjects in the first age cohort, and monitoring of serum calcium and phosphorus will continue according to the planned schedule, ie, days 1, 10, and 30, and months 3, 6, 12, 18, 24, 30, and 36, thereafter.

Dosing may be delayed if a subject has bone surgery scheduled. Dosing with denosumab can be continued after the surgery at the investigator's discretion.

6.2.3.2 3-Month Dosing Regimen

Serum calcium to be measured at day 10 and day 30 after the week 12 and week 24 doses.

6.3 Other Protocol-required Therapies

All other protocol-required supplements, including calcium and vitamin D, that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these drugs.

All subjects are recommended to take daily supplements of 30-50 mg/kg and not to exceed 1000 mg elemental calcium and at least 800 IU vitamin D during the study. If a subject becomes hypercalcemic, hypercalciuric or has other intolerance over the course of the study, the calcium and/or vitamin D supplementation may be modified or discontinued at investigator discretion and site will manage supplementation to maintain normal serum and urine calcium. Similarly, 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.

Alternative therapy for OI is at investigator discretion and consistent with local standard of care and clinical practice guidelines.

Additional details regarding these supplements are provided in the IPIM.

6.4 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], AST, ALT, TBL) and/or international normalized ratio [INR] and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen IP 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 Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Denosumab and other protocol-required therapies, as appropriate, should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2x 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	> 3x ULN

- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; 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 (NASH)
  - Non-hepatic causes (eg, rhabdomylosis, hemolysis)

6.4.2 Criteria for Conditional Withholding of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following rules are recommended for withholding of denosumab and other protocol-required therapies*:*

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

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

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

Denosumab and other protocol-required therapies, *as appropriate,* should be withheld pending investigation into alternative causes of DILI. If IP(s) is withheld, the subject is to be followed according to recommendations in Appendix A 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 (Section 6.4.3).

6.4.3 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 and other protocol-required therapies, as appropriate 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.

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, combination product,** or device after it is released for distribution to market or clinic by either **(1)** Amgen or **(2)** distributors and partners for whom Amgen manufactures the material. **This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.**

This includes any investigational products described above provisioned and/or repackaged/modified by Amgen.

Any product complaint associated with **products described above and** supplied by Amgen are to be reported according to the instructions provided in the **modular** IPIM.

6.7 Excluded Treatments and/or Procedures During Study Period

All medications listed in the exclusion criteria, shown in Table 6-1 below, or any other medication that is known or suspected to have activity on bone metabolism (except, calcium and vitamin D) will not be allowed during the study while the subject is on IP.

Table 6-1. List of Proscribed Therapy

Aluminum	Calcium chelators	Lithium
Anabolic steroids	Chemotherapeutics	Parathyroid hormone (or a derivative)
Androgens	Chronic heparin use (> 7 days) (LMWH are permitted)[a]	Progestins, other than when used as monotherapy for contraception
Anticonvulsants (gabapentin and benzodiazepines are allowed)	Cinacalcet	Prolonged glucocorticoid therapy at a prednisone equivalent dose of ≥ 5.0 mg/day (tapering glucocorticoid courses of ≤ 1 month duration are permitted regardless of dose; inhaled or topical glucocorticoids are permitted)
Any investigational agents for bone loss other than study drug	Citrated products	
Aromatase inhibitors	Fluoride[b]	
Biologics (except for insulins and vaccines)	Gonadotropin-releasing hormone agonists	
Bisphosphonates	Growth hormone (unless stable for at least 3 months prior to screening)	
Calcitonin	Immunosuppressants	
		Protease inhibitors
		Strontium
		Tibolone

LMWH = low molecular weight heparin
[a] Low molecular weight heparin does not have the same effect on bone density or fracture, and thus is not prohibited.
[b] Fluoride taken for routine dental care is permitted.

6.8 Contraceptive Requirements

6.8.1 Female Subjects

Female subjects of childbearing potential must agree to practice true sexual abstinence (refrain from heterosexual intercourse) or use a highly effective method of contraception during treatment and for an additional 5 months after the last dose of denosumab.

Contraceptive methods that achieve a failure rate of less than 1% per year when used consistently and correctly are considered highly effective and may include: Hormonal (combined estrogen and progestogen or progestogen-only) contraception associated with inhibition of ovulation (oral, injectable, implantable, intravaginal, or transdermal route); intrauterine device (IUD); intrauterine hormonal releasing system (IUS); bilateral tubal occlusion; vasectomized partner (provided that partner is the sole sexual partner of the female participant and the vasectomized partner has received medical assessment of the surgical success); true sexual abstinence when this is in line with the preferred

and usual lifestyle of the subject. The reliability of sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject.

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 urine pregnancy testing prior to their IP administration at every visit and EOS.

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 Male and 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 amenorrhoea method.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 7-1. Schedule of Assessments for 6-Month Dosing Regimen

	Screening Phase	Treatment Phase									
		Study Day			Study Months						
	Screening	1	10	30	3	6	12	18	24	30	36/ET[g]
Procedures			± 3 day window		These visits will have a ± 7 day window						
Informed consent	X										
Medical history	X										
Physical examination	X	X			X	X	X	X	X	X	X
Tanner stage	X					X[j]	X	X[j]	X	X[j]	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Height	X						X		X		X
Weight	X	X				X	X	X	X	X	X
Armspan	X						X		X		X
DXA (AP lumbar spine)[k]		X[a]				X	X	X	X		X
DXA (proximal femur – total hip and femoral neck in subjects ≥ 5 years of age at screening)[k]		X[a]				X	X	X	X		X
X-ray (lateral thoracic, lumbar spine)[k]		X[l]					X		X		X
X-ray – AP knees[b,k]		X				X	X	X	X	X	X
Dental X-ray (cephalogram and panoramic radiograph)[k]		X									X
Oral visual inspection							X		X		
Dental X-ray (molars)[c,k]							X		X		
Hematology	X	X			X	X	X	X	X	X	X
Serum chemistry	X	X	X	X[i]	X	X	X	X	X	X	X
Serology for HIV, hepatitis B and hepatitis C[h]	X										
25(OH) vitamin D level	X										

Footnotes defined on last page of the table

Table 7-1. Schedule of Assessments for 6-Month Dosing Regimen

	Screening Phase	Treatment Phase									
		Study Day			Study Months						
	Screening	1	10	30	3	6	12	18	24	30	36/ET[g]
Procedures			± 3 day window		These visits will have a ± 7 day window						
Pregnancy test (urine dipstick method)[d]	X	X				X	X	X	X	X	
SC injection of denosumab (1 mg/kg)		X				X	X	X	X	X	
Dispensation of calcium and vitamin D		X				X	X	X	X	X	
Antidenosumab antibody assay		X					X		X		X
Concomitant medications		X	X	X	X	X	X	X	X	X	X
PK (serum denosumab)[e]		X	X	X[e]	X[e]	X	X	X	X	X	X
BTM (BSAP, sCTX)[e]		X	X	X[e]	X[e]	X	X	X	X	X	X
Safety data collection/ recording/reporting[f]		X	X	X	X	X	X	X	X	X	X
Clinical fracture recording		←									→
Administration of:											
CHQ-PF-50		X					X		X		X
CHAQ Disability Score		X					X		X		X
WBFPRS		X					X		X		X

Footnotes defined on next page

AP = anteroposterior; BSAP = bone-specific alkaline phosphatase; BTM = bone turnover markers; CHAQ = Childhood Health Assessment Questionnaire; CHQ-PF-50 = Child Health Questionnaire-Parent Form-50; DXA = dual-energy X-ray absorptiometry; EOS = End of Study; ET = end of treatment; HIV = human immunodeficiency virus; PI = principal investigator; PK = pharmacokinetic; SC = subcutaneous; sCTX = serum type I collagen C-telopeptide; WBFPRS = Wong-Baker Faces Pain Rating Scale

[a] To be performed in duplicate at this visit only

[b] To be performed only in children with open growth plates who do not have bilateral hardware

[c] To be performed only if a delay in molar eruption is suspected by the PI

[d] To be performed in female subjects who have had menarche or those who are Tanner stage 2 or higher

[e] Serum denosumab concentrations and BTM (BSAP and sCTX) levels will be collected at day 30 and month 3 only in a PK/BTM substudy of approximately 50 subjects

[f] Only serious adverse events will be collected at screening visit. Both serious and nonserious adverse events will be collected at study day 1 visit and later

[g] See Section 7.2.5 for details on EOS visit.

[h] Serology for HIV and hepatitis B and C should be performed on a separate day from the other non-fasting blood draws for screening in subjects with body weight ≤ 11 kg

[i] 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/BTM sub-study. 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.

[j] Tanner stage to be conducted in female subjects only at months 6, 18, and 30 to determine the need to perform a pregnancy urine dipstick test at these visits.

[k] All images/reports (as applicable) to be sent to the central imaging vendor. Additional spine x-rays should be obtained if clinically indicated.

[l] For subjects who have not otherwise qualified based on fracture criteria, the baseline lateral spine radiograph may be obtained at the screening visit.

[m] Subjects will have 1 EOS visit, either at the end of 6-Month Dosing Regimen or at the end of 3-Month Dosing Regimen. All subjects who remain on study (have not previously completed Month 36/EOS under the 6-Month Dosing Regimen) will be eligible to transition to the 3-Month Dosing Regimen. Subjects may be consented and transition to the 3-Month Dosing Regimen up to and including the date they attend for a Month 36 visit under the 6-Month Dosing Regimen. For subjects who have completed Month 30 on the 6-Month Dosing Regimen, an EOS will not be performed if the subject re-consents to the 3-Month Dosing Regimen.

Table 7-2. 6-Month Dosing Regimen Additional Schedule of Assessments for Subjects in Sentinel Cohort and the First 5 Subjects Who Have Increased Bone Turnover as Defined in Section 3.1

Procedures	Day 2	Day 3	Day 4	Day 6	Day 8	Day 12	Day 14
Serum calcium and phosphorus[a]	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Safety data collection/recording/reporting	X	X	X	X	X	X	X

[a] Blood collection may be performed by a qualified individual at the subject's home in lieu of a site visit; If blood collection is performed at the subject's home on day 2 through day 14, it should occur at no more than 2 consecutive visits at a time. 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.

Table 7-3. 6-Month Dosing Regimen Additional Schedule of Assessments for Subjects in Sentinel Cohort as Defined in Section 3.1

	Study Month					
Procedures	4.5	10	16	22	28	34
Serum calcium	X	X	X	X	X	X
BTM (BSAP and sCTX)	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Safety data collection/recording/reporting	X	X	X	X	X	X

BSAP = bone-specific alkaline phosphatase; BTM = bone turnover markers; sCTX = serum type I collagen C-telopeptide

Table 7-4. Schedule of Assessments for 3-Month Dosing Regimen

		Treatment Phase												
	Q3M Day 1[a]	Study Day			Study Weeks									
		Q3M D10	Q3M D30	Q3M D60	Q3M W12	D10	D30	Q3M W24	D10	D30	Q3M W36	Q3M W48[b]	Additional Dosing[c]	EOS/ ET[d]
Procedures		± 3 day window			Day visits have a ± 3 day window; week visits have a ± 7 day window									
Re-consent to Q3M	X													
Physical examination	X				X			X			X	X	X	X
Tanner stage	X				X[e]			X[e]			X[e]	X[e]	X[e]	X[e]
Vital signs	X	X	X	X	X			X			X	X	X	X
Height	X				X			X			X	X	X	X
Weight	X				X			X			X	X	X	X
Armspan	X											X		X
DXA (AP lumbar spine)[f]	X[g]							X				X		X
DXA (proximal femur – total hip and femoral neck in subjects ≥ 5 years of age at screening)[f]	X							X				X		X
X-ray (lateral thoracic, lumbar spine)[f]	X											X		X
X-ray – AP knees[f, h]	X							X				X		X
Dental X-ray (cephalogram and panoramic radiograph)[f]	X													X
Oral visual inspection	X				X			X			X	X	X	X
Dental X-ray (molars)[f, i]	X													
Hematology	X				X			X			X	X	X	X
Serum chemistry	X	X	X		X	X[j,l]	X[j,l]	X	X[j,l]	X[j,l]	X	X	X	X
25(OH) vitamin D level	X													

Footnotes defined on the last page of the table

Table 7-4. Schedule of Assessments for 3-Month Dosing Regimen

		Treatment Phase												
	Q3M Day 1[a]	Study Day			Study Weeks									
		Q3M D10	Q3M D30	Q3M D60	Q3M W12	D10	D30	Q3M W24	D10	D30	Q3M W36	Q3M W48[b]	Additional Dosing[c]	EOS/ ET[d]
Procedures		± 3 day window			Day visits have a ± 3 day window; week visits have a ± 7 day window									
Urine calcium	X				X			X			X	X	X	X
Pregnancy test (urine dipstick method)[k]	X				X			X			X	X	X	X
SC injection of denosumab (1 mg/kg)	X[l]				X[l]			X[l]			X[l]	X[l,m]	X[l]	
Dispensation of calcium and vitamin D	X				X			X			X	X	X	
Antidenosumab antibody assay	X											X		X
Concomitant medications	X	X	X	X	X			X			X	X	X	X
PK (serum denosumab)	X	X[l]	X[l]	X[l]	X			X			X	X	X	X
BTM (BSAP, sCTX)[n]	X	X	X	X	X			X			X	X	X	X
Safety data collection/ recording/reporting	X	X	X	X	X			X			X	X	X	X
Clinical fracture recording	X	X	X	X	X			X			X	X	X	X
Administration of:														
CHQ-PF-50	X											X		**X**
CHAQ Disability Score	X											X		**X**
WBFPRS	X											X		**X**

Footnotes defined on next page

AP = anteroposterior; BSAP = bone-specific alkaline phosphatase; BTM = bone turnover markers; CHAQ = Childhood Health Assessment Questionnaire; CHQ-PF-50 = Child Health Questionnaire-Parent Form-50; D = day; DXA = dual-energy X-ray absorptiometry; EOS = End of Study; ET = end of treatment; PI = principal investigator; PK = pharmacokinetic; Q3M = every 3 months (every 12 weeks); SC = subcutaneous; sCTX = serum type I collagen C-telopeptide; W = week; WBFPRS = Wong-Baker Faces Pain Rating Scale

[a] The 3-Month Dosing Regimen day 1 is defined as the date of reconsent and the first dose of denosumab on the 3-Month Dosing Regimen. All subjects who remain on study (have not previously completed Month 36/EOS under the 6-Month Dosing Regimen) will be eligible to transition to the 3-Month Dosing Regimen unless they ended treatment due to an adverse event. Subjects may be consented and transition to the 3-Month Dosing Regimen up to and including the date they attend for a Month 36 visit under the 6-Month Dosing Regimen.

[b] Week 48 will be EOS for all subjects who are at or beyond M24 of 6-Month Dosing Regimen at time of transition to 3-Month Dosing Regimen. End of Study will be delayed for subjects at M18 of 6-Month Dosing Regimen at time of transition to 3-Month Dosing Regimen. These subjects will complete additional Dosing visits at W48 and W60. End of Study will be delayed until W72. **End of study may be extended for some subjects until week 84 due to 24 weeks of safety follow-up following the last dose of IP due to urgent safety measure.**

[c] Performed only for subjects at M18 of 6-Month Dosing Regimen at time of transition to 3-Month Dosing Regimen, and who will not have completed a minimum of 144 weeks (Month 36) on study if EOS is scheduled 3 months after week 48. These subjects will receive additional dosing at W48 and W60 so that EOS occurs at week 144 (W72 on 3-Month Dosing Regimen). All other subjects will perform EOS at W48. **End of study may be extended for some subjects until week 84 due to 24 weeks of safety follow-up following the last dose of IP due to urgent safety measure.**

[d] See Section 7.2.5 for details on EOS visit. Week 48 will be EOS for all subjects who are at or beyond M24 of 6-Month Dosing Regimen at time of transition to 3-Month Dosing Regimen. All W48 and EOS procedures will be performed during this visit. No IP will be administered. End of Study will be delayed for subjects at M18 of 6-Month Dosing Regimen at time of transition to 3-Month Dosing Regimen. These subjects will complete additional Dosing visits at W48 and W60. End of Study will be delayed until W72. **End of study may be extended for some subjects until week 84 due to 24 weeks of safety follow-up following the last dose of IP due to urgent safety measure.**

[e] Tanner stage to be conducted in female subjects at every dosing visit and EOS to determine the need to perform a pregnancy urine dipstick test. For a female who has a Tanner stage 2 or greater, or has had menarche, a pregnancy test will be performed prior to IP administration at every visit and EOS.

[f] All images/reports (as applicable) to be sent to the central imaging vendor, including any unscheduled images taken during the study. Additional spine x-rays should be obtained if clinically indicated.

[g] To be performed in duplicate on Day 1 of 3-Month Dosing Regimen.

[h] To be performed only in children with open growth plates who do not have bilateral hardware.

[i] To be performed only if a delay in molar eruption is suspected by the PI.

[j] Serum calcium to be performed on days 10 and 30 following week 12 and week 24 doses. Blood collection may be performed by a qualified individual at the subject's home, in lieu of a site visit.

[k] To be performed in female subjects who have had menarche or those who are Tanner stage 2 or higher.

[l] At all study visits signs and symptoms of hypocalcemia will be assessed and subjects reminded of importance of taking calcium and vitamin D.

[m] Week 48 denosumab administration performed only for subjects who will not have completed a minimum of 144 weeks (Month 36) on study. Applies to subjects who were at M18 of 6-Month Dosing Regimen at time of transition to 3-Month Dosing Regimen.

[n] On days 10, 30, and 60, blood collection may be performed by a qualified individual at the subject's home for these visits, in lieu of a site visit. In addition, when blood collection is performed at the subject's home, the investigator must ensure that concomitant medications, clinical fractures, and adverse events, if any, are appropriately recorded.

Table 7-5. Schedule of Assessments Following Implementation of Urgent Safety Measure

(For Subjects on 3-Month Dosing Still On Study as of 30 September 2021)

Weeks after last dose of denosumab (Week 0)[a]	Week 12[b]	Week 24/EOS[c]
Physical examination	X	X
Tanner stage	X	X[e]
Vital signs	X	X
Height	X	X
Weight	X	X
Armspan		X
DXA (AP lumbar spine)[d]		X
DXA (proximal femur – total hip and femoral neck in subjects ≥ 5 years of age at screening)[d]		X
X-ray (lateral thoracic, lumbar spine)[d]		X
X-ray – AP knees[d, e]		X
Dental X-ray (cephalogram and panoramic radiograph)[d]		X
Oral visual inspection	X	X
Dental X-ray (molars)[d, f]	X	X
Hematology	X	X
Serum chemistry[g]	X	X

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Footnotes defined on last page of table

Table 7-5. Schedule of Assessments Following Implementation of Urgent Safety Measure
(For Subjects on 3-Month Dosing Still On Study as of 30 September 2021)

Weeks after last dose of denosumab (Week 0)[a]	Week 12[b]	Week 24/EOS[c]
Urine calcium	X	X
Pregnancy test (urine dipstick method)[h]	X	X
Dispensation of calcium and vitamin D[i]	X	X
Antidenosumab antibody assay	X	X
Concomitant medications	X	X
PK (serum denosumab)	X	X
BTM (BSAP, sCTX)	X	X
Safety data collection/ recording/reporting	X	X
Clinical fracture recording	X	X
Administration of:		
CHQ-PF-50[j]		X
CHAQ Disability Score[j]		X
WBFPRS[j]		X

Footnotes defined on next page.

AP = anteroposterior; BSAP = bone-specific alkaline phosphatase; BTM = bone turnover markers; CHAQ = Childhood Health Assessment Questionnaire; CHQ-PF-50 = Child Health Questionnaire-Parent Form-50; D = day; DXA = dual-energy X-ray absorptiometry; PK = pharmacokinetic; (every 12 weeks); sCTX = serum type I collagen C-telopeptide; W = week; WBFPRS = Wong-Baker Faces Pain Rating Scale

[a] **No IP will be administered. Subjects who have been on alternative therapy for more than 6 months, subjects whose last dose was between 12 and 24 weeks ago, and subjects whose last dose of IP was greater than 24 weeks ago should complete their EOS visit, and no 24-week safety follow-up is required. These subjects can follow the current protocol and complete the EOS CRF.**

[b] **Not to be completed for subjects who have already completed 24 weeks post IP.**

[c] **End of study may be extended for some subjects until week 84 due to the 24 weeks of safety follow-up following the last dose of IP due to urgent safety measure.**

[d] **All images/reports (as applicable) to be sent to the central imaging vendor, including any unscheduled images taken during the study. Additional spine x rays should be obtained if clinically indicated. Assessment may not be performed if less than 3 months have elapsed since previous radiographic assessment.**

[e] **To be performed only in children with open growth plates who do not have bilateral hardware.**

[f] **To be performed only if a delay in molar eruption is suspected by the PI.**

[g] **If the 12-week visit occurs after any of the first 3 injections of IP, serum calcium should be obtained at day 10 and day 30 after that visit.**

[h] **To be performed in female subjects who have had menarche or those who are Tanner stage 2 or higher.**

[i] **Per investigator discretion.**

[j] **Administration of PROs may not be performed if less than 1 month has elapsed since the previous assessment.**

7.2 General Study Procedures

Study tests and procedures will be performed only after written informed consent and subject assent (as applicable by local law) is obtained. During the study, every effort should be made to keep subjects on the study schedule of procedures. Tests and procedures will be performed as per the schedule provided in Section 7.1.

All subjects enrolled in the trial will have samples assayed for antidenosumab binding and if positive, neutralizing antibodies.

The injectable IP administration should be the last procedure performed at each visit after all other study procedures have been completed.

Specific details of all tests and procedures are outlined below

Study Visit Definitions

6-Month Dosing Regimen:

- The screening date is defined as the date the informed consent/subject assent is signed.
- Enrollment date is defined as the date of enrollment call is made using IVRS/IWRS.
- Day 1 visit must occur within 35 days of screening or 42 days of the rescreening date.
- Day 1 is defined as the day that the initial dose of IP is administered to the subject. All subjects should receive their first dose of the IP on the day of enrollment. If this is not possible, day 1 must occur within 72 hours of enrollment.

3-Month Dosing Regimen:

- 3-Month Dosing Regimen day 1 should occur at the next study visit following all regulatory and ethics approval of protocol Amendment 5 dated 11 March 2020.
- 3-Month Dosing Regimen day 1 visit is defined as the day that the initial dose of IP for 3-Month Dosing Regimen is administered to the subject.
- 3-Month Dosing Regimen will be defined as 12 weeks per dose period.

If a subject's visit is delayed, his/her subsequent visit dates should not be shifted, but always calculated based on the day 1 visit date.

Visit Schedule following Urgent Safety Measure:

Following implementation of the Urgent Safety Measure, subsequent visits are calculated from last dose of IP.

Study Visit Windows

6-Month Dosing Regimen: **(Note: Per urgent safety measure, all dosing should be stopped).**

- All tests and procedures scheduled for day 1 must occur within 35 days of the screening date or 42 days of the rescreening date.
- All tests and procedures scheduled for the day 10 and day 30 visits must be performed within ± 3 days of the scheduled visit date**.**
- All tests and procedures scheduled for the month 3, 6, 12, 18, 24, 30, and 36 visits must be performed within ± 7 days of the scheduled visit date.
- All tests and procedures for the additional visits for the sentinel cohort must be performed on the day of the scheduled visit date.

3-Month Dosing Regimen: **(Note: all 3-Month dosing has been stopped even if subjects have not met the study duration.)**

- All tests and procedures scheduled for the day 10, day 30, and day 60 visits must be performed within ± 3 days of the scheduled visit date.
- All tests and procedures scheduled for the week 12, 24, 36, 48 visit and any additional dosing months must be performed within ± 7 days of the scheduled visit date.
- 3-Month Dosing Regimen will continue for 12-months of dosing, or longer for any subjects who would not meet the minimum of week 144 (Month 36) at time of EOS.

Any missed visits, tests not done, and examinations not conducted must be reported as such on the electronic case report forms (eCRFs).

Study procedures for a specific visit may be completed on multiple days as long as all of the procedures are completed within the visit window. However, the IP should be administered last.

7.2.1 Screening and Enrollment

Screening and Enrollment applies only to the 6-Month Dosing Regimen and initial enrollment into this study. 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; see below).

Before obtaining informed consent/subject assent, the investigator should discuss alternative therapies that may be available.

The following procedures are to be completed during the timepoints designated in the Schedule of Assessments (Section 7.1).

- Confirmation that the ICF and the Assent Form 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
- Physical examination as per standard of care (including medical/surgical history and fracture history)
- Tanner stage
- Height in centimeters measured without shoes
- Weight
- Armspan
- Vital signs (ie, pulse, respiration rate, temperature, systolic and diastolic blood pressure)
- Laboratory assessments hematology, serum chemistry, serology for HIV, hepatitis B and hepatitis C, and 25 (OH) vitamin D level
    - Serology for HIV and hepatitis B and C should be performed on a separate day from the other non-fasting blood draws for screening in subjects with body weight ≤ 11 kg
- Urine pregnancy test
- Documentation of medication history

7.2.1.1 Enrollment in IVRS/IWRS System/Rescreening

Rescreening applies only to the 6-Month Dosing Regimen and initial enrollment into this study. 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 either of the 2 conditions below. Sites will be notified, near to 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.

7.2.1.1.1 Rescreening for Serum 25 (OH) Vitamin D

Rescreening applies only to the 6-Month Dosing Regimen and initial enrollment into this study. Rescreening will be allowed for subjects with an initial screening serum 25 (OH) vitamin D level of < 20 ng/mL (< 49.9 nmol/L). Rescreening, if needed for serum vitamin D level, will be performed as follows:

- Enter the subject as a screen failure into the IVRS/IWRS System and immediately enter him/her as a rescreen. Subjects not entered into IVRS/IWRS System 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 ≥ 20 ng/mL (≥ 49.9 nmol/L) obtained by the central laboratory prior to day 1 visit.

- Subjects must restart a new 42-day rescreening window. Repletion treatment and a confirmatory lab result must be obtained within this 42-day window to meet subject eligibility requirements.
- Subjects may be rescreened only once for either vitamin D or full rescreening (defined below).

Sites will be notified, near to 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 test for serum vitamin D levels will be screen failed.

7.2.1.1.2 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 not applicable anymore.

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, and hepatitis C, in subjects who are rescreened more than 84 days of screen failure.
- Subjects must be enrolled within the new 42-day rescreening window.

Subjects may be rescreened only once for either vitamin D or full rescreening.

7.2.2 Transition to 3-Month Dosing Regimen

Subjects who already transitioned will immediately follow the Schedule of Assessments for Urgent Safety Measure as outlined in Table 7-5.

7.2.3 Treatment

As of 30 September 2021, due to the life-threatening risk of hypercalcemia, subjects on study who had not completed their EOS visit were immediately discontinued from IP, and will be followed for safety for 24 weeks following the last dose of IP per the updated Schedule of Assessments (Table 7-5). The last dose of IP will be considered week 0. Subjects who have been on alternative therapy for more than 6 months or whose last dose of IP was greater than 24 weeks, no additional 24-week safety follow-up is required. These subjects can follow the previous protocol (protocol amendment 6) and complete the EOS CRF. Subjects whose last dose was between 12 and 24 weeks ago can complete the EOS assessments at week 24 per the updated Schedule of Assessments (Table 7-5). The following procedures will be completed during the treatment period at

the times designated in the Schedule of Assessments **(Section 7.1)**. Denosumab (1 mg/kg and up to a maximum of 60 mg) should be administered last during each visit that it is required.

- Physical examination as per standard of care
- Tanner stage
- Height in centimeters measured without shoes
- Weight
- Armspan
- Vital signs (ie, pulse, respiration rate, temperature, systolic and diastolic blood pressure)
- Laboratory assessments hematology, serum chemistry, and urine calcium
- Assessment of antidenosumab antibodies
- Assessment of serum denosumab levels
- BTM (sCTX and BSAP)
- DXA Assessments of the lumbar spine and proximal femur, conducted every 6 months
- Urine pregnancy test must be performed for female subjects with a Tanner stage 2 or greater, or have had menarche prior to IP administration and EOS
- X-ray radiograph of the spine, conducted every 12 months
- X-ray radiograph of the knees, conducted every 6 months
- Oral visual inspection (dental X-ray may be obtained if a delay in molar eruption is suspected by the PI)
- Dental X-ray (cephalogram, panoramic)
- Concomitant medication recording
- Clinical fracture recording
- Adverse event collection/recording/reporting
- Serious adverse event collection/recording/reporting
- Administration of PROs (CHQ-PF-50, CHAQ, WBFPRS)
- Dispense calcium and vitamin D
- SC injection of denosumab

7.2.4 Study Procedures

As of 30 September 2021, due to the life-threatening risk of hypercalcemia, subjects on study who had not completed their EOS visit were immediately discontinued from IP, and will be followed for safety for 24 weeks following the last dose of IP per the updated Schedule of Assessments (Table 7-5). The last dose of IP will be considered week 0. Subjects who have been on alternative

therapy for more than 6 months or whose last dose of IP was greater than 24 weeks, no additional 24-week safety follow-up is required. These subjects can follow the previous protocol (protocol amendment 6) and complete the EOS CRF. Subjects whose last dose was between 12 and 24 weeks ago can complete the EOS assessments at week 24 per the updated Schedule of Assessments (Table 7-5).

Data Collection

All laboratory values will be electronically transferred from the central laboratory to the Amgen database. The central imaging vendor will collect DXA data and radiographic imaging and will electronically transfer the data to the Amgen database. All other data will be captured on the eCRF.

Medical and Medication History

Medical and medication history will be obtained prior to enrollment and will be recorded on the eCRF.

Physical Examination

The physical examination will include height and weight. A pelvic, breast, or rectal examination is not required unless a specific evaluation is warranted. Height measurements (in centimeters without shoes) will be performed in the standing position unless it is not possible to do so. In instances where standing height cannot be measured, measurement of recumbent height will be allowed.

Vital Signs

The following measurements should be performed: systolic and diastolic blood pressure (if clinically acceptable by the investigator), pulse, respiratory rate, and temperature. Subject should be in a supine position in a rested and calm state for at least 5 minutes before pulse assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

Armspan

The arm span is measured with the child leaning against a flat surface (eg, wall) with the arms outstretched (or extended to the best of the child's ability) parallel to the ground at

shoulder height, and between the tip of the middle fingers of the left and right hands. The flat surface should have a fixed point against which the child places 1 middle finger and a mark should be made on the surface for the opposite middle finger. The child then steps away and the distance between the fixed point and the new mark is measured and recorded.

Pregnancy Test

Pregnancy tests will be performed from urine samples to be collected at screening, on day 1, at every IP administration visit (prior to denosumab injection), and EOS 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).

Radiographic Assessments

Lateral spine radiographs obtained within the past 2 years prior to screening can be submitted for verification of prevalent vertebral compression fracture. Nonvertebral 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. Baseline lateral spine radiographs will be obtained on day 1 for all enrolled subjects unless an adequate lateral spine radiograph has been obtained within the past 2 months prior to screening day. For subjects who have not otherwise qualified based on fracture criteria, the baseline lateral spine radiograph may be obtained at the screening visit.

For the purposes of this study, fractures related to OI are not considered pathological fractures, however pathological will relate to fractures in this disease of interest. Lateral spine radiographs will be obtained at the day 1 visit for 3-Month Dosing Regimen, and every 12 months.

All available radiographic assessments for evaluation of potential fracture from screening until EOS, including any unscheduled assessments, will be submitted to 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.

3-Month Dosing Regimen assessments will be compared to data from 6-Month Dosing Regimen as pretreatment.

Dual-energy X-Ray Absorptiometry Assessments

All subjects will undergo bone densitometry assessments of the lumbar spine and subjects 5 years of age or older at screening will undergo bone densitometry assessments of the proximal femur (for total hip and femoral neck) performed by DXA per the schedule outlined in **Section 7.1**.

.Scans will be performed every 6 months.

A DXA should be performed at day 1 visit (in duplicate) of the 3-Month Dosing Regimen, and then every 6-months.

Only General Electric Lunar or Hologic bone densitometers will be allowed for this study. The same DXA machine will be used for all study procedures for a particular subject. Any changes to DXA machines should follow the requirements specified in the Imaging Manual. The left side should be used for proximal femur, unless prohibited (eg, hip implant). If another side must be used or is inadvertently used during Day 1, 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.

Spine Radiographs

Lateral radiographs of the thoracic and lumbar spine will be obtained to determine morphometric fractures.

Knee Radiograph

In subjects with open growth plates, 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 one with the higher Z-score at day 1 of 6-Month Dosing Regimen, unless prohibited by presence of hardware, in which case an AP radiograph of the contralateral knee may be obtained.

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, 3-Month Dosing Regimen day 1 visit, and end of the study (to be performed only if a delay in molar eruption is suspected by the PI).

Other Dental Radiograms

As indicated below (see "Oral Visual Inspection"), 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 assessment should be submitted to the central reader.

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 all visits for the 3-Month Dosing Regimen to assess the risk for unerupted molars. The subject should be referred to a dentist to perform radiographic assessment of the unerupted molar(s) (see above "Other Dental Radiograms**"**) if:

- A subject is 7 years of age or older 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).

Blood and Serum Assessments

All blood samples will be obtained by venipuncture before IP administration. The average volume of blood drawn per visit will be approximately 5.0 mL.

6-Month Dosing Regimen:

In subjects undergoing intensive serum calcium and phosphorus monitoring on days 2, 3, 4, 6, 8, 10, 12, and 14 after study drug administration, the blood volume drawn per visit for these assessments will be approximately 2.2 mL.

Blood will be obtained for the following assessments (Table 7-7) at the timepoints outlined in the Schedule of Assessments (Section 7.1) The date and time of blood collection will be recorded in the subjects' medical records.

Given the lack of denosumab PK data in pediatric patients, denosumab PK will be collected in all subjects in this study in order to adequately characterize denosumab exposure and variability within the different age cohorts, as specified below.

6-Month Dosing Regimen: serum denosumab concentration

- Samples for serum denosumab concentration levels will be obtained on days 1 and 10, and months 6, 12, 18, 24, 30, and 36 in all subjects, with additional serum PK samples to be collected at day 30 and month 3 in a PK/BTM substudy of approximately 50 subjects, as outlined on the Schedule of Assessments (**Section 7.1**)

3-Month Dosing Regimen: serum denosumab concentration

- Samples for serum denosumab concentration levels will be obtained at predose on day 1 of the 3-Month Dosing Regimen and on days 10, 30, and 60, and every 3 months (ie, W12, W24, W36, W48, etc.) until EOS, as outlined on the Schedule of Assessments (Table 7-4).

Laboratory Assessments

All blood samples will be processed and sent to the central laboratory. The central laboratory will be responsible for completing assays and shipping samples to Amgen for performance of other assays. **Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).**

6-Month Dosing Regimen:

- In addition, blood samples collected from the sentinel cohort for assessment of serum calcium and phosphorus in the first 14 days after denosumab administration will be sent to the local laboratory and the central laboratory. In

addition, blood samples collected from the sentinel cohort for assessment of serum calcium at months 4.5, 10, 16, 22, 28 and 34 after denosumab administration will be sent to central laboratory. Blood samples collected for assessment of serum calcium and phosphorus in the first 14 days after denosumab administration from the first 5 subjects of any age who have increased bone turnover, as defined in Section 3.1.1, will be sent to the local laboratory and central laboratory on days 2, 3, 4, 6, 8, 12, and 14, if body weight is ≥ 11 kg, but only to the local laboratory for subjects whose body weight is < 11 kg.

- Collection of blood samples may be performed at the subject's home at visits occurring on days 2, 3, 4, 6, 8, 12, 14, and 30, as applicable. House visits between days 2 and 30, if performed, should occur at no more than two consecutive visits at a time. 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. Collection of blood samples may not be performed at the subject's home on day 30 in subjects participating in the PK/BTM substudy. The collection of blood samples may not be performed at the subject's home either at months 4.5 and 10, due to the collection requirements for the BTM samples obtained during these visits.

3-Month Dosing Regimen

- Serum chemistry should be collected at Day 10 and Day 30 following first administration in 3-Month Dosing Regimen. Additional assessments of serum calcium will be performed on day 10 and day 30 after the week 12 and week 24 doses. Blood collection may be performed by a qualified individual at the subject's home, in lieu of a site visit.
- PK and BTM will be collected at days 10, 30, and 60 and every 3 months.
- Blood collection may be performed by a qualified individual at the subject's home, in lieu of a site visit, on days 10, 30, and 60. When blood collection is performed at the subject's home, the investigator must ensure that concomitant medications, clinical fractures, and adverse events, if any, are appropriately recorded.

The central laboratory will be responsible for all serum chemistry, vitamin D, hematology as well as serology assessments and will also conduct assessments of sCTX and serum BSAP. Amgen will be responsible for antidenosumab antibody assessments. The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all serum samples.

All samples will be obtained by venipuncture before IP administration, when applicable. The date and time of blood collection will be recorded in the subject's medical record.

Table 7-7 outlines the specific analytes for the serum chemistry and hematology assessments, as well as other assessments to be conducted on blood samples.

Table 7-7. Blood Sample Analyte Listing

Serum Chemistry	Hematology	Other Assessments
Sodium	Red blood cells	samples for antidenosumab antibody assay
Potassium	Hemoglobin	25 (OH) vitamin D
Chloride	Platelets	sCTX
Bicarbonate	White blood cells	BSAP
Total protein	Differential	Serum denosumab concentrations
Albumin	Neutrophils	Urine calcium
Calcium[a,b]	Eosinophils	Urine or serum pregnancy test
Albumin-corrected calcium	Basophils	
Magnesium	Lymphocytes	
Phosphorus[a]	Monocytes	
Glucose		
BUN	Serology	
Creatinine	HIV-1, -2 antibody	
Total Bilirubin	Hepatitis B surface antigen	
Alkaline phosphatase	Hepatitis C antibody	
AST (SGOT)		
ALT (SGPT)		

ALT (SGPT) = **a**lanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = **a**spartate aminotransferase (serum glutamic oxaloacetic transaminase); BSAP = **b**one**-**specific alkaline phosphatase; BUN = **b**lood urea nitrogen; HIV = human immunodeficiency virus; sCTX = serum type I collagen C-telopeptide.

[a] (6-Month Dosing Regimen) will be measured in local and central laboratory for the first 14 days in the sentinel cohort; will be measured in local and central laboratory (as applicable) for the first 14 days in the first 5 subjects of any age who have increased bone turnover, as defined in Section 3.1.1.

[b] (6-Month Dosing Regimen) will be measured at the central laboratory at months 4.5, 10, 16, 22, 28, and 34 in the sentinel cohort

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 or trade name, indication, quantity administered (dose and frequency) and date(s) of administration will be recorded. For other concomitant therapies being taken, data collection may be limited to generic drug name/treatment, indication and dates of administration.

Additional Procedures Conducted in Sentinel Cohort Only (6-Month Dosing Regimen)

Intensive mineral homeostasis assessment: Serum calcium and phosphorus concentrations will be closely monitored during the study. In order to better evaluate and characterize the risk for hypocalcemia and hypophosphatemia, intensive monitoring of

mineral homeostasis will be implemented in the first 5 subjects enrolled in the study. Serum calcium and phosphorus concentrations will be checked daily at the local laboratory for the first 3 days after administration of the first dose of denosumab and every other day thereafter for a total of 14 days in this 5-subject sentinel cohort.

If no safety concerns arise from dosing of the sentinel cohort over the first 14 days after the first administration of denosumab, enrollment will be opened for the remainder of the subjects in the study, and monitoring of serum calcium and phosphorus will continue according to the planned schedule, ie, days 1, 10, and 30, and months 3, 6, 12, 18, 24, 30, and 36, thereafter. However, based on the results from the sentinel cohort, serum calcium and/or phosphorus monitoring may be performed more frequently in the remainder of the subjects enrolled in the study, if warranted.

A similar approach will be employed in the first 5 subjects of any age who have increased bone turnover, defined as meeting 2 of the 3 following criteria: (1) untreated with bisphosphonates for 4 years prior to entry in the trial; (2) Type 3 OI with the following characteristics: height $< 3^{rd}$ percentile and bowed extremities (or saber shins); or (3) Tanner stage 3 or 4.

Furthermore in order to better characterize the theoretical risk of rebound hypercalcemia during the latter part of the dosing interval, additional monitoring of serum calcium also will be implemented in the first 5 subjects enrolled in the study (sentinel cohort). Serum calcium concentrations will be checked at months 4.5, 10, 16, 22, 28**,** and 34 in the 5-subject sentinel cohort. Based on these results from the sentinel cohort, serum calcium monitoring may be performed similarly in the remainder of the subjects enrolled in the study, if warranted.

Patient-reported Outcomes

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

The CHQ 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 CHQ (CHQ-PF-50) will 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.

The scale 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.

Safety Data

Subjects will be evaluated for safety events at each study visit through EOS. If the subject is removed from IP, every effort should be made to continue evaluating safety events through his/her last study visit. See Section 8.4 for details regarding safety data collection/recording/reporting.

7.2.5 Safety Follow-up Visit(s)/End of Study Visit

As of 30 September 2021, due to the life-threatening risk of hypercalcemia, subjects on study who had not completed their EOS visit were immediately discontinued from IP, and will be followed for safety for 24 weeks following the last dose of IP per the updated Schedule of Assessments (Table 7-5). The last dose of IP will be considered week 0. Subjects who have been on alternative therapy for more than 6 months or whose last dose of IP was greater than 24 weeks, no additional 24-week safety follow-up is required. These subjects can follow the previous protocol (protocol amendment 6) and complete the EOS CRF. Subjects whose last dose was between 12 and 24 weeks ago can complete the EOS assessments at week 24 per the updated Schedule of Assessments (Table 7-5).

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

- Procedures involving X-ray radiation other DXA assessment may not be performed if less than 3 months have elapsed since the previous radiographic assessment
- Administration of PROs may not be performed if less than 1 month has elapsed since the previous assessment

7.3 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected at day 1, annually and EOS/early termination (ET) (Schedule of Assessments, **Section 7.1**) 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.

7.4 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Section 7.1) 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 informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the biology of OI, the dose response and/or prediction of response to denosumab to characterize antibody response (if any), and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from these analyses 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 such 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 IP 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 IP or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (**Section 7.1**) 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).

Ongoing subjects **as of 30 September 2021** who have **been** discontinued **from** IP (denosumab) **as a result of the urgent safety measure, and subjects who have previously discontinued IP** and/or other 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, collection/reporting of serious adverse events, and/or collection of outcome data. **Following implementation of the urgent safety measure, subjects should be followed for 24 weeks for safety following the last dose of IP.** If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 7.4 for further details).

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, publicly available data

can be included after withdrawal of consent. The investigator is to discuss with the subject/subjects parent or legal guardian 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 IP and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion. **Following identification of a life-threatening risk of hypercalcemia, a decision has been made to stop all IP administration and subjects will be followed for safety for 24 weeks.**

8.3 Reasons for Removal From Treatment, or Study

8.3.1 Reasons for Removal From Treatment

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

- subject request
- adverse event
- decision by sponsor
- death
- lost to follow-up
- other protocol-specified criteria:
  - pregnancy
  - disease flare requiring treatment not allowed in the protocol (eg, colitis, asthma)
  - decline in lumbar spine BMD Z-score by at least 0.5 units at any 6-month assessment compared to the 3-Month Dosing Regimen baseline
  - 4 or more new long bone and/or vertebral fractures in any 6 month period (additional spine x rays should be obtained if clinically indicated)
  - 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 consistent with local institutional guidelines
  - 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.
  - severe or symptomatic hypercalcemia, which requires the use of a rescue medication for management
  - dental abnormalities requiring invasive dental procedures, as determined by **i**nvestigator and/or treating dentist and within the local institutional practice guidelines
    - Denosumab administration should be withheld 30 days prior to an invasive dental procedure and until complete mucosal healing is observed and documented (refer to Section 6.2.3 for guidance on restarting IP)
  - ONJ

8.3.2 Reasons for Removal From Study

Reasons for removal from protocol-required IP or procedural assessments include any of the following:

- withdrawal of consent from study
- death
- lost to follow-up
- decision by sponsor

8.4 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

For subjects who are lost to follow-up, the investigator can search publicly 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.

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.

A single event should be reported for each increased level of severity on the adverse event 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 or subject's legally acceptable representative that occur after first dose of IP (denosumab) through the **safety follow-up (SFU)/**EOS are reported using the applicable eCRF (eg, Adverse Event Summary).

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),
- Severity [and/or toxicity per protocol],
- Assessment of relatedness to the IP (denosumab) or other protocol-required therapies or any study procedures/study activity, and
- Action taken.

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE). The grading scale used in this study is described in Appendix A. The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

The investigator must assess whether the adverse event is possibly related to the IP (denosumab) and/or other protocol-related 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 IP (denosumab)?"

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of IP, protocol-required therapies, and/or procedure (including any screening procedure(s)). 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, 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, or subject's legally acceptable representative, that occur after signing of the informed consent through 30 days after the last dose of IP or **SFU/**EOS, whichever is later, 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 applicable CRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an Electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix 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 IP (denosumab) 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 IP (denosumab) and/or other protocol-related therapies?"

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 record. Information

provided about the serious adverse event must be consistent with that recorded on the applicable CRF (eg, Adverse Event Summary CRF).

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

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.

Adverse events that are adjudicated as positive for ONJ will be categorized as serious adverse events and will follow the serious adverse events reporting as noted above.

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

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

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting. **If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.**

9.3 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 obtain information about adverse event occurrence.

9.4 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

9.5 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 after the last dose of denosumab through an additional 5 months.

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 will 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 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.

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.

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur 5 months after the last dose of protocol-required therapies.

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 will be requested.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

Primary Endpoint:

- Change from baseline in lumbar spine BMD Z-score, as assessed by DXA, at 12 months in subjects receiving the 3-Month Dosing Regimen

Secondary Endpoint(s):

- Change from baseline in lumbar spine BMD Z-score, as assessed by DXA, at 6 months in subjects receiving the 3-Month Dosing Regimen
- Change from baseline in proximal femur BMD Z-score, as assessed by DXA, at 6 and 12 months (in subjects 5 years of age and older) in subjects receiving the 3-Month Dosing Regimen
- Incidence of X-ray confirmed long bone and new and worsening vertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Incidence of X-ray confirmed new and worsening vertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Incidence of X-ray confirmed new vertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Incidence of improving vertebral fractures from **baseline of 3-**Month Dosing Regimen to 12 months on 3-Month Dosing Regimen
- Incidence of vertebral and nonvertebral fractures from last 12 months on 6-Month Dosing Regimen to 12 months on 3-Month Dosing Regimen (in subjects 5 years of age or older)
- Change from baseline in CHQ-PF-50 Physical Summary score at 12 months in subjects receiving the 3-Month Dosing Regimen
- Change from baseline in CHQ-PF-50 Psychological Summary score at 12 months in subjects receiving the 3-Month Dosing Regimen
- Change from baseline in CHAQ Disability Index score at 12 months in subjects receiving the 3-Month Dosing Regimen
- Change from baseline in WBFPRS at 12 months in subjects receiving the 3-Month Dosing Regimen
- Change from baseline in growth velocity (determined by calculating age-adjusted Z-scores for height, weight and BMI) at 12 months in subjects receiving the 3-Month Dosing Regimen
- Serum concentration of denosumab and serum BTM on days 1, 10, 30, 60, and every 3 months in subjects on 3-Month Dosing Regimen

Exploratory Endpoints:

[redacted]

[redacted]

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
- Subject incidence of metaphyseal index Z-score above age-appropriate normal range
- Subject incidence of abnormal molar eruption
- Subject incidence of abnormal mandibular shaping
- Subject incidence of hypercalcemia

10.1.2 Analysis Sets

10.1.2.1 Full Analysis Set

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

10.1.2.2 DXA Analysis Set

The DXA analysis set includes all subjects in the FAS with baseline and ≥ 1 postbaseline DXA assessment on 3-Month Dosing Regimen for the endpoint of interest (lumbar spine and proximal femur) as provided by the central imaging vendor**.**

10.1.2.3 Vertebral Fracture Analysis Set

The vertebral fracture analysis set includes all subjects in the FAS who have a readable non-missing baseline and ≥ 1 non-missing postbaseline X-ray vertebral evaluation on 3-Month Dosing Regimen as provided by the central imaging vendor. This analysis set will be used to analyze incidence of vertebral fracture endpoints.

10.1.2.4 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 ≥ 1 postbaseline valid PRO response on 3-Month Dosing Regimen for the appropriate PRO. Moreover, the CHQ-PF-50 analysis set will only include subjects 5 years of age and older at screening; the questionnaire has not been validated in younger children (4 years of age or younger), and so this subgroup will not be included in the CHQ-PF-50 analysis set.

10.1.2.5 Growth Velocity Analysis Set

The analysis set includes all subjects in the FAS who have evaluable data (age in total months, and weight, height, and BMI) at baseline and ≥ 1 post baseline assessment for each growth velocity endpoint (weight-for-age, height-for-age, and BMI-for-age Z-scores).

10.1.2.6 Metaphyseal Analysis Set

This analysis set includes all subjects in the 3-month dosing safety analysis set with open growth plates (and no hardware preventing accurate calculation of metaphyseal index) at baseline and X-ray of the knee at baseline and post-baseline.

10.1.2.7 6-Month Dosing Regimen Safety Analysis Set

The safety analysis set includes all subjects in the FAS who received ≥ 1 dose of IP.

10.1.2.8 3-Month Dosing Regimen Safety Analysis Set

The 3-Month Dosing Regimen safety analysis set includes all subjects in the FAS who received ≥ 1 dose of 3-Month Dosing.

10.1.2.9 PK Analysis Set

The PK analysis set includes all subjects in the 3-Month Dosing Regimen safety analysis set who have ≥ 1 serum denosumab reported result 3-Month Dosing Regimen.

10.1.2.10 PK Substudy Analysis Set

The subset includes all subjects in the 6-Month Dosing Regimen safety analysis set who enroll in the PK/BTM substudy and have ≥ 1 serum denosumab reported result.

10.1.2.11 BTM Analysis Set

The BTM analysis set includes all subjects in the 3-Month Dosing Regimen safety analysis set who have baseline and ≥ 1 postbaseline assessments for the endpoint of interest on 3-Month Dosing Regimen.

10.1.2.12 BTM Substudy Analysis Set

The subset includes all subjects in the safety analysis set who enroll in the PK/BTM substudy and have baseline and ≥ 1 postbaseline assessments for the endpoint of interest on 6-Month Dosing Regimen.

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 will be investigated.

- Age (years) at the time of transition to 3-Month Dosing Regimen
- Baseline lumbar spine BMD Z-score of 3-Month Dosing Regimen

10.1.3.2 Subgroups

The following subgroups will be explored for the change from baseline of 3-Month Dosing Regimen in lumbar spine BMD Z-score as assessed by DXA at 12 months.

- Gender (females vs males)
- Age at the time of screening (2 to 4, 5 to 10, 11 to 17 years)
- OI severity subgroups

10.2 Sample Size Considerations

10.2.1 6-Month Dosing Regimen

A study sample size of 150 subjects will be enrolled to collect adequate efficacy and safety information for the ad hoc analysis at 12 months. Assuming that 20% of subjects will not be evaluable at month 12 for the ad hoc efficacy endpoint due to dropout, the analysis set for the ad hoc efficacy endpoint will include at least 120 subjects.

10.2.2 3-Month Dosing Regimen

Sixty previously enrolled subjects **were previously transitioned** to a 3-Month Dosing Regimen. **A**pproximately **60** previously enrolled subjects **were to** transition to a 3-Month Dosing Regimen.

This sample size will provide more than 95% power to demonstrate that the difference in the change from baseline lumbar spine BMD Z-score at month 12 between denosumab and historical control is significantly greater than zero using 1-sample 2-sided t-test with a significance level of 0.05 based on the following assumptions:

- Mean change in lumbar spine BMD Z-score at 12 months for denosumab is 1.31 (SD = 0.91), which represents the lower bound of the 95% CI for the effect of a bisphosphonate (zoledronic acid) (EMA assessment report for Zometa Procedure no EMEA/H/C/000336/II/0031)
- Weighted mean (SE) change in lumbar spine BMD Z-score at 12 months for historical control is 0.01(0.09) (95% CI: -0.17, 0.18), estimated using meta-analysis

based on data from the placebo or control of 3 studies in children with OI (Ward et al, 2011; Rauch et al, 2009; Letocha et al, 2005).

Assuming the sample size will provide at least 10% of the subjects evaluable for the primary efficacy endpoint in most subgroups of interest, the effect of denosumab on lumbar spine BMD Z-score also may be summarized descriptively in these subgroups.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Not applicable; this is an open-label single-arm study.

10.4 Planned Analyses

10.4.1 Primary Analysis

The primary analysis (or final analysis since there is only 1 milestone analysis for this study) will occur after **the last subject** complete**s the 24-week safety follow up visit following the last dose of IP**.

10.4.2 Data Monitoring Committee

Safety of the subjects during study conduct will be monitored by the study team and a DMC in an ongoing manner. A charter specifying the DMC functions will be written with the agreement of the DMC members. Independent experts may be invited to Open Sessions to support in DMC review, as needed.

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 of 3-Month Dosing Regimen in BMD Z-score at 12 months in subjects on 3-Month Dosing Regimen will be analyzed based on the DXA analysis set using repeated measures analysis with visit (6 and 12 months), baseline age, and baseline BMD Z-score as fixed effects. Visit will be treated as a categorical variable. Missing baseline and postbaseline BMD Z-scores will not be imputed. The estimated 12-month least squares (LS) mean will be presented with a 95% CI. The estimated 12-month LS mean will be compared to weighted estimated mean (SE) of 0.01 (0.09) from historical controls (Ward et al, 2011; Rauch et al, 2009; Letocha et al, 2005) using a 1-sample 2-sided t-test.

Summary statistics will be provided by the subgroups defined in Section 10.1.3.2.

10.5.3 Secondary Efficacy Endpoint(s)

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

For each skeletal site (lumbar spine, total hip, and femoral neck), change from baseline of 3-Month Dosing Regimen in BMD Z-score in subjects on 3-Month Dosing Regimen will be analyzed using repeated measures analysis with visit (6 and 12 months), baseline age, and baseline BMD Z-score as fixed effects. Visit will be treated as a categorical variable. Missing baseline and postbaseline BMD Z-scores will not be imputed. LS mean and 95% CI will be presented for each visit.

All analyses will be based on the DXA analysis set corresponding to the skeletal site of interest. Total hip and femoral neck summaries will include only subjects 5 years of age and older at screening.

10.5.3.2 New and Worsening Fractures, and Vertebral and Nonvertebral Fractures

On-treatment fracture rates in subjects on 3-Month and 6-Month Dosing Regimen **will be summarized**. Pretreatment data includes 12 months prior to 3-Month Dosing Regimen denosumab administration for vertebral and nonvertebral fractures. Subgroup analyses may be conducted depending on the number of subjects in each subgroup.

Exposure-adjusted Incidence rate (EAIR) for fractures pre and post 3-Month Dosing Regimen will be provided.

The incidence of vertebral fractures will be summarized based on the vertebral fracture analysis set and the incidence of nonvertebral fractures will be summarized based on the FAS with the fracture assessment provided by the central imaging vendor.

The incidence of long bone and new and worsening fractures and vertebral and nonvertebral fractures in subjects on 3-Month Dosing Regimen will be summarized based on the FAS with the fracture assessment provided by the central imaging vendor.

10.5.3.3 Improved Vertebral Fracture

The proportion of subjects with improved vertebral fracture from baseline of 3-Month Dosing Regimen will be summarized at each timepoint based on the vertebral fracture analysis set on 3-Month Dosing Regimen.

10.5.3.4 Patient-reported Outcomes

Patient-reported outcomes (CHQ-PF-50, CHAQ disability index score and WBFPRS) and their changes from 3-Month Dosing Regimen will be summarized at month 12 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 of 3-Month Dosing Regimen in age-adjusted growth velocity endpoints will be summarized at 12 months based on the growth velocity analysis set. There is no imputation for missing data.

10.5.3.6 Serum Denosumab Concentrations

Serum denosumab concentrations will be summarized by visit based on PK analysis set on 3-Month Dosing Regimen for all subjects and on 6-Month Dosing Regimen for the PK/BTM substudy. There will be no imputation for missing values.

10.5.3.7 Bone Turnover Markers

Actual values and percent changes from baseline of 3-Month Dosing Regimen in each parameter (BSAP and sCTX) will be descriptively summarized at each visit based on the BTM analysis set for the parameter of interest. There will be no imputation for missing values.

Similar analyses also including day 30 and month 3 will be performed based on the BTM substudy analysis set based on 6-Month Dosing Regimen.

10.5.4 Safety Endpoints

All safety endpoints will be summarized for all subjects on 6-Month Dosing Regimen and subjects who received ≥ 1 dose of 3-Month Dosing Regimen separately.

10.5.4.1 Adverse Events

All adverse events will be summarized based on the 3-Month Dosing Regimen safety analysis set and 6-Month Dosing Regimen 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 IP and treatment-emergent adverse events of interest will also be provided. In addition, the exposure-adjusted subject incidence on the 3-Month Dosing Regimen safety analysis set and 6-Month Dosing Regimen safety analysis set respectively will be summarized.

In addition, the following selected adverse events will be summarized:

- 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

- Severe or symptomatic hypocalcemia
- ONJ
- Abnormal molar eruption
- Abnormal mandibular shaping
- Hypercalcemia

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 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 CTCAE v4.03.

All laboratory analyses will be based on the 3-Month Dosing Regimen safety analysis set and 6-Month Dosing Regimen safety analysis set. Subjects with missing data for a scheduled visit will not contribute to the tabulation for that timepoint (no imputation).

10.5.4.3 Vital Signs

Descriptive statistics of the actual values and changes from baseline in vital signs (pulse, respiration rate, temperature, systolic and diastolic blood pressure) will be presented by visit based on the 3-Month Dosing Regimen safety analysis set and 6-Month Dosing Regimen safety analysis set. Subjects with missing data for a scheduled visit will not contribute to the tabulation for that timepoint (no imputation).

10.5.4.4 Antidenosumab Antibodies

Immunogenic response during the study will be described by tabulating the numbers and percentages of subjects who tested positive for (binding and neutralizing) antidenosumab antibodies based on the 3-Month Dosing Regimen safety analysis set and 6-Month Dosing Regimen safety analysis set.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

Investigators should have communicated the Urgent Safety Measure findings and actions to all ongoing subjects by phone or in-person within 3 days of the receipt of the Dear Investigator Letter, and documented this contact in the subject's medical records. A written consent/assent will be provided to subjects, following approval by the IRB/IEC, and subjects will be asked to sign this written consent/assent form.

An initial sample ICF and pediatric subject assent form is provided for the investigator to prepare the informed consent document and subject assent to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent and subject assent documents are 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 IP(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. If the subject reaches the age of consent during the duration of the study, once the subject reaches the age of maturation (usually 18), the previously acquired parental consent is no longer applicable and the participant's consent must be obtained. Per International Conference on 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.

The investigator also is responsible for obtaining written assent from the pediatric subject as applicable by local law, before any protocol-specific screening procedures or any IP(s) is/are administered.

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.

For this study, assent from the child and consent from the parents or legally authorized representatives must be obtained, except if the child is a neonate, an infant, a toddler or very young as defined by local law. 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. Country-specific requirements should be followed for specific local information.

Where permitted according to country regulation, the ICF will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, subject assent form, 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, ICF and subject assent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen IP.

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 **that Amgen distributes to the site**. 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.

During the course of the study, if new information becomes available that alters the benefit**:**risk of the study or the study drug, Amgen will follow applicable regulations to notify investigators, the IRB/IEC, and regulatory authorities, as appropriate.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- 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
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the US Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

11.3 Subject Confidentiality

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

The subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

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 age (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.

Subject data should be kept in a secure location. Access to subject data will be limited to authorized individuals, as described below.

In compliance with Federal regulations/ICH 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.

Amgen complies with all relevant and applicable laws and regulations that protect personal information in order to ensure subject confidentiality and privacy. Subjects are designated by a unique subject identification number in the sponsor's systems. The sponsor uses access-controlled systems to house, review and analyze subject data. These systems are backed-up regularly to minimize the risk of loss of subject data; procedures are also defined for data recovery in the event of data loss. The sponsor has standard operating procedures in place that restrict access to subject data to those who require access to this data based on their role and have also completed the required training. These procedures also outline the process for revoking access to such data when it is no longer needed. In the event of a security breach, the sponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter 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

As of 30 September 2021, due to the life-threatening risk of hypercalcemia, subjects on study who had not completed their EOS visit were immediately discontinued from IP, and will be followed for safety for 24 weeks following the last dose of IP per the updated Schedule of Assessments (Table 7-5). Subjects who have been on alternative therapy for more than 6 months or whose last dose of IP was greater than 24 weeks, no additional 24-week safety follow-up is required. These subjects can follow the previous protocol (protocol amendment 6) and complete the EOS CRF. Subjects whose last dose was between 12 and 24 weeks ago can complete the EOS assessments at week 24 per the updated Schedule of Assessments (Table 7-5).

If Amgen amends the protocol, agreement from the investigator must be obtained. 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 to Amgen.

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 study contract. 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.

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 eCRFs will be included on the Amgen Delegation of Authority Form.

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

In this study, the IVRS/IWRS captures the following data points and these are considered source data: subject identification number and enrollment number.

eCRF entries may be considered source data if the eCRF is the site of the original recording (ie, there is no other written or electronic record of data). In this study, PRO CRFs can be used 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.

Elements to include:

- Subject files containing completed eCRFs, ICFs, and subject identification list
- Study files containing the protocol with all amendments, Denosumab Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.

In addition, all original source documents supporting entries in the eCRFs 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, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen clinical monitor is responsible for verifying the eCRFs 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 eCRFs.

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 eCRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing 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, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and readily available.
- Updates to eCRFs 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 and/or site notifications 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. This signature indicates that investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

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 (Section 7.1).

the investigator can search publicly 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

eCRFs 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

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publication**s** 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.

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.

If permitted under applicable regional laws or regulatory guidelines, subjects may be compensated for other inconveniences not associated with study-related injuries (eg, travel costs).

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

CTCAE (Adverse Event Grading Scale)

Drug-induced Liver Injury Reporting & 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, Adverse Event 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 9.1.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product (IP)(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Sections 6.4.1 and 6.4.2 or who experience AST or ALT elevations $>$ 3 x ULN 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 Serious Adverse Event Report Form

AMGEN **Study # 20130173** Prolia (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?						Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						Denosumab No✓	Denosumab Yes✓	<Device> No✓	<Device> Yes✓	<Device> No✓	<Device> Yes✓	<Device> No✓	<Device> Yes✓		
				☐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

IP/Amgen Device:		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 #
Denosumab	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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AMGEN **Study # 20130173** Prolia (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 # 20130173** Prolia (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 -	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.		

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 FAX#

1. Case Administrative Information

Protocol/Study Number: 20130173

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm___ / dd___ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm___/dd___/yyyy____

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

If yes, provide product (or study drug) stop date: mm___/dd___/yyyy____

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

5. Pregnancy Information

Pregnant female's LMP mm___ / dd___ / yyyy____ ☐ Unknown

Estimated date of delivery mm___ / dd___ / yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm___ / dd___ / yyyy____

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

If yes, provide date of delivery: mm___ / dd___ / yyyy____

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

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

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

Print Form

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: 20130173

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:** _____

Effective Date: 03 April 2012, version 2.

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Amendment 7

Protocol Title: Prospective, Multicenter, Single-arm Study to Evaluate Efficacy, Safety, and Pharmacokinetics of Denosumab in Children With Osteogenesis Imperfecta

Amgen Protocol Number AMG 162 20130173

NCT Number: NCT03638128

Amendment Date:	22 October 2021
Superseding Amendment Date	26 November 2021

Rationale:

This protocol is being amended to:

- Address Risk Level 1 safety concern of hypercalcemia. Per Amgen decision based on the Data Monitoring Committee (DMC) recommendation and urgent safety measure, the protocol has been updated to stop treatment and subjects will continue to a 24-week safety follow up period.
- Update risks and benefits to reflect that the benefit of AMG 162 does not outweigh the risks
- Add language that all subjects will discontinue study treatment and be followed for safety for 24 weeks
- Add Schedule of Assessments for safety follow-up period
- Administrative and editorial updates

On 26 November 2021, the protocol amendment 7 was superseded to:

- Add week 12 visits for oral visual inspection, sample collection for hematology and serum chemistry, and clinical fracture recording.
- Remove the administration of the Child Health Questionnaire-Parent Form-50 (CHQ-PF-50), Childhood Health Assessment Questionnaire (CHAQ) Disability Score and Wong-Baker Faces Pain Rating Scale (WBFPRS) at week 12.

Amendment 7

Protocol Title: Prospective, Multicenter, Single-arm Study to Evaluate Efficacy, Safety, and Pharmacokinetics of Denosumab in Children With Osteogenesis Imperfecta

Amgen Protocol Number AMG 162 20130173

NCT Number: NCT03638128

Amendment Date: 22 October 2021

Rationale:

This protocol is being amended to:

- Address Risk Level 1 safety concern of hypercalcemia. Per Amgen decision based on the Data Monitoring Committee (DMC) recommendation and urgent safety measure, the protocol has been updated to stop treatment and subjects will continue to a 24-week safety follow up period.
- Update risks and benefits to reflect that the benefit of AMG 162 does not outweigh the risks
- Add language that all subjects will discontinue study treatment and be followed for safety for 24 weeks
- Add Schedule of Assessments for safety follow-up period
- Administrative and editorial updates

- Clarify inconsistencies in BTM endpoints
- Make minor administrative and editorial changes

Superseding Amendment 6

Protocol Title: Prospective, Multicenter, Single-arm Study to Evaluate Efficacy, Safety, and Pharmacokinetics of Denosumab in Children With Osteogenesis Imperfecta

Amgen Protocol Number (AMG162) 20130173

EudraCT Number: 2014-000184-40

Amendment Date:	19 November 2020
Superseding Amendment Date:	14 January 2021

Superseding Amendment 6 Summary of Changes:

Rationale:

Protocol amendment 6 is being superseded to correct inconsistencies introduced into the document during amendment 6. Additionally, administrative, typographical, and formatting changes were made throughout the protocol.

Amendment 6

Protocol Title: Prospective, Multicenter, Single-arm Study to Evaluate Efficacy, Safety, and Pharmacokinetics of Denosumab in Children With Osteogenesis Imperfecta

Amgen Protocol Number (AMG162) 20130173

EudraCT Number: 2014-000184-40

Amendment Date: 19 November 2020

Rationale:

The protocol is being amended to harmonize content with protocol 20170534 and to address FDA feedback received. In addition, this amendment is intended to optimize study procedures to improve the operational efficiency of the protocol following team feedback.

Changes include, but are not limited to:

- Additional blood samples at days 10 and 30 following investigational product dosing at weeks 12 and 24.
- Administrative changes from previously written memos.
- Analyte table updated.
- Statistical Analysis section updated.
- Administrative, typographical and formatting changes were made throughout the protocol. Updates have been implemented to align with the current template.

Amendment 5

Protocol Title: Prospective, Multicenter, Single-arm Study to Evaluate Efficacy, Safety, and Pharmacokinetics of Denosumab in Children With Osteogenesis Imperfecta

Amgen Protocol Number (AMG 162 [Denosumab]) 20130173

Amendment Date: 11 March 2020

Rationale:

The main purpose of this protocol amendment is to adjust the dose regimen from 6-Month Dosing Regimen to 3-Month Dosing Regimen for evaluation in paediatric OI subjects.

Amendment 4

Protocol Title: Prospective, Multicenter, Single-arm Study to Evaluate Efficacy, Safety, and Pharmacokinetics of Denosumab in Children With Osteogenesis Imperfecta

Amgen Protocol Number (AMG 162) 20130173

EudraCT Number: 2014-000184-40

Amendment Date: 24 March 2016

Rationale:

The protocol is being amended to:

- Update secondary objectives and endpoints and exclusion criteria language to reflect approved modifications to the Paediatric Investigation Plan
- Eliminate all occurrences of “randomization” in the study procedures as it does not apply to the protocol design
- Update rescreening language to clarify requirements and rescreening guidelines
- Update pregnancy and lactation reporting language to align with recent changes to the protocol template and Core Risk and Discomforts form, and replace sample reporting forms with current versions
- Update safety language to adhere to recent changes to the protocol template, and replace sample electronic serious adverse event reporting forms with current versions
- Correct typographic, grammatical, and formatting errors throughout the protocol.

Amendment 3

Title: Prospective, Multicenter, Single-arm Study to Evaluate Efficacy, Safety, and Pharmacokinetics of Denosumab in Children With Osteogenesis Imperfecta

Amgen Protocol Number (AMG 162) 20130173

Amendment Date: **11 February 2015**

Rationale:

The protocol is being amended to:

- update visit schedules for enabling assessment of serum calcium

The higher bone turnover rates expected at baseline in children with osteogenesis imperfect (OI) may increase the risk for rebound hypercalcemia in the latter part of the denosumab dosing interval due to release of bone turnover inhibition. Additional visits at months 4.5,10, 16, 22, 28 and 34 will be conducted in the first 5 subjects enrolled in the sentinel cohort in order to assess the effect of denosumab on serum calcium homeostasis and to permit adaptation of subsequent mineral homeostasis assessments for all study subjects as appropriate.

Minor administrative changes and clarifications have also been incorporated.

Additions are noted in **bold** text.

Amendment 2

Protocol Title: Prospective, Multicenter, Single-arm Study to Evaluate Efficacy, Safety, and Pharmacokinetics of Denosumab in Children With Osteogenesis Imperfecta

Amgen Protocol Number (AMG 162) 20130173

Amendment Date: **28 August 2014**

Rationale:

The protocol is being amended to:

- update the exclusion criteria regarding serum vitamin D levels at screening and duration of prior use of PTH or PTH derivatives
- remove blood pressure measurement as a required procedures
- add the potential of some visits being conducted by sending qualified personnel to obtain blood samples

The exclusion criteria are being amended to modify the requirement for serum vitamin D in order to make it consistent with other protocols in the denosumab program and to clarify duration of exposure to PTH or PTH derivatives.

Blood pressure monitoring is being removed as a required procedure since it may expose the subjects to the risk of fracturing their bone during assessment.

To reduce the burden on the subject of having to visit the clinic site too often, some of the visits over the first 30 days after denosumab injection may be performed by sending qualified personnel to the subject.

Typographic and administrative changes were made throughout the document as needed.

Amendment 1

Protocol Title: Prospective, Multicenter, Single-arm Study to Evaluate Efficacy, Safety, and Pharmacokinetics of Denosumab in Children With Osteogenesis Imperfecta

Amgen Protocol Number (AMG 162) 20130173

Amendment Date: **25 July 2014**

Rationale:

The protocol is being amended to conform to feedback received from the Voluntary Harmonization Process of regulatory agencies in Europe

- update the exclusion criteria
- add serological tests at screening visit
- clarify follow up of subjects with incident severe or symptomatic hypocalcemia
- clarify that pregnancy is a stand-alone criteria for discontinuation of study drug
- enumerate the acceptable methods of contraception

The exclusion criteria is being amended to add an item to make it consistent with the summary of product characteristics (SPC) in effect in the European Union (EU). Serological tests for HIV and Hepatitis B and Hepatitis C are being added to be consistent with exclusion criteria outlined in the protocol.

The protocol also is being amended to clarify treatment and follow up of subjects who discontinue study drug as a result of severe or symptomatic hypocalcemia; to state that pregnancy is an independent reason for discontinuation of study drug.

Acceptable methods of contraception are being outlined in the protocol and are consistent with those listed in the informed consent form.