Title Page

Protocol Title:		Multicenter, Single-arm Open-label Extension Study to Assess Long-term Safety and Efficacy of Current or Prior Treatment With Denosumab in Children/Young Adults With Osteogenesis Imperfecta
Short Protocol Title:		Open-label Extension of Study 20130173 of Denosumab in Children and Young Adults with Osteogenesis Imperfecta
Protocol Number:		20170534
Investigational Product:		Denosumab
Trade Name:		Prolia
Sponsor	**Name of Sponsor:**	Amgen Inc.
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EudraCT Number:		2018-000550-21
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Version/Date:		**Data Element Standards Version** Version 5.0; 20 March 2015

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).

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled Multicenter, Single-arm Open-label Extension Study to Assess Long-term Safety and Efficacy of Current or Prior Treatment With Denosumab in Children/Young Adults With Osteogenesis Imperfecta, dated **02 February 2022**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, 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) and my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

Table of Contents

List of Tables

List of Figures

1. Protocol Synopsis

Protocol Title: Multicenter, Single-arm Open-label Extension Study to Assess Long-term Safety and Efficacy of Current or Prior Treatment With Denosumab in Children/Young Adults With Osteogenesis Imperfecta

Short Protocol Title: Open-label Extension of Study 20130173 of Denosumab in Children and Young Adults with Osteogenesis Imperfecta

Study Phase: 3

Indication: Osteogenesis Imperfecta (OI)

Rationale

Study 20170534 **was** an open-label extension of Study 20130173 to assess long-term safety and efficacy of current or prior treatment with denosumab in children/young adults with osteogenesis imperfecta (OI). This study **was** required for compliance with key binding elements from the denosumab Pediatric Investigational Plan (PIP) for Study 20130173. All subjects who complete**d** end of study (EOS) on Study 20130173, regardless of whether they received investigational product until the last protocol-specified dose on the 20130173 study or ended investigational product early, **were** offered participation in a long-term open-label follow-up study – where this protocol **had** been approved at the site. Subjects who **withdrew** consent/assent to transition to 3-Month Dosing Regimen on 20130173 **were** also offered participation in **the** study. When subjects in Study 20130173 near**ed** the EOS visit (completion), subjects **were** offered participation in Study 20170534. If a subject **was** rolled over into the 20170534 study, they **were** offered to receive alternative treatment including commercial denosumab every 6 months (6-Month Dosing Regimen) or **would** be observed without any treatment or the investigational product given every 3 months (3-Month Dosing Regimen).

Starting from 30 September 2021, due to the life-threatening events of hypercalcemia reported on denosumab use in the pediatric OI study, **it was decided** not **to dose** any **subject further** on **Study** 20170534 and **to follow all subjects** for safety for 24 weeks following the last dose of denosumab **as part of an urgent safety measure**.

Rationale for Protocol Amendment 5

Given the limited amount of available data for efficacy analysis, the analysis of the secondary endpoints is changed to ensure only quality data is presented as an endpoint. The secondary efficacy endpoints of fracture and growth velocity are removed, and BMD Z-score is clarified given the multiple treatment sequences in

the trial. Adverse events of fracture, including femur fractures, will be presented in the adverse event tables.

The primary objective and endpoint is safety and is unchanged.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate long-term safety of denosumab in subjects with pediatric osteogenesis imperfecta (OI) completing Study 20130173	• The primary endpoints are subject incidence of adverse events, serious adverse events, and adverse events of special interest, subject incidence of antidenosumab antibodies, changes from baseline in laboratory values and vital signs, and subject incidence of metaphyseal index Z-score above age-appropriate normal range, abnormal molar eruption, and mandibular shaping
Secondary	
• To describe changes in bone mineral density (BMD) of lumbar spine and proximal femur (total hip and femoral neck) from baseline to **6,** 12**, and 24** months	• Actual values and changes in BMD Z-score of lumbar spine and proximal femur (total hip and femoral neck) from Study 20170534 baseline, as assessed by dual X-ray absorptiometry (DXA), at **6,** 12**, and 24** months

Hypotheses

This study is descriptive in nature and does not involve testing formal hypotheses.

Overall Design

Recently, life-threatening events of hypercalcemia were reported on denosumab 1 mg/kg Q3M regimen in the pediatric OI subjects within 20130173 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 and decided to stop the 20170543 study for any further enrollment or dosing with denosumab.

Per the 30 September 2021 Dear Investigator Letter (DIL), all investigators were notified to immediately stop denosumab treatment and continue the study as per the normal Schedule of Activities (without denosumab treatment). All subjects participating in the study will be followed for 24 weeks after their last dose of denosumab. At 24 weeks the EOS Assessments should be completed per the current Schedule of Activities (Table 2-1).

Subjects who were on denosumab (3 months or every 6 months treatment) and stopped denosumab more than 24 weeks ago should be scheduled for their EOS Visit at the next

scheduled visit and have their EOS Visit assessments conducted per the current Schedule of Activities (Table 2-1).

Subjects on alternative or observational therapy that have never taken denosumab should complete the EOS assessments at the next scheduled visit (Table 2-1).

Study 20170534 is an open-label, prospective, extension study of Study 20130173 to assess long-term safety and efficacy of current or prior treatment with denosumab in children/young adults with OI. This study is required for compliance with key binding elements from the denosumab PIP for Study 20130173. All subjects who complete EOS on Study 20130173, regardless of whether they received investigational product until the last protocol-specified dose on the 20130173 study or ended investigational product early, are offered participation in a long-term open-label follow-up study – where this protocol has been approved at the site. Subjects who withdraw consent/assent to transition to 3-Month Dosing Regimen on 20130173 will also be offered participation in this study. When subjects in Study 20130173 near the EOS visit (completion), subjects will be offered participation in Study 20170534. If a subject is rolled over into the 20170534 study, they will be offered to receive alternative treatment including commercial denosumab every 6 months (6-Month Dosing Regimen) or will be observed without any treatment or the investigational product given every 3 months (3-Month Dosing Regimen).

Number of Subjects

The number of subjects in this study will be determined by the number of subjects completing Study 20130173, and who are willing and able to participate in the long-term follow-up study.

Summary of Subject Eligibility Criteria

Any subject enrolled in Study 20130173 and completed the study, or EOS visit regardless of completing or ending investigational product early.

For a full list of eligibility criteria, please refer to Section 6.1 and Section 6.2.

Treatments

On the 3-Month Dosing Regimen, calcium and vitamin D were dispensed as a protocol-required therapy. For subjects on alternative therapies including the 6-Month Dosing Regimen, calcium and vitamin D were not protocol-required therapies and used at the investigator's discretion and local standard of care in pediatric OI. After the Urgent Safety Measure, all subjects are on alternative therapy with the exclusion of the 6-Month Dosing Regimen and are to use calcium and vitamin D at the site's discretion, and consistent with the local standard of care.

Subjects may receive denosumab at a 3-Month Dosing Regimen, alternative osteoporosis medication/s of investigator's choice administered per local standard of care (including commercial denosumab at a 6-Month Dosing Regimen) or observation only (no intervention). Subjects on denosumab at a 3-Month Dosing Regimen will be dispensed calcium and vitamin D.

Procedures

After signing informed consent/assent for this study, demographics and all medical history (including medical history of fracture and OI, and resolved adverse events [including fractures]) will be carried over from Study 20130173. Clinically relevant resolved adverse events will be manually added at investigator discretion into the medical history case report form (CRF) and resolved fracture events will also be added to fracture history. Ongoing events (including fractures) at screening will be added to CRF pages for Study 20170534. The standard assessments of physical examination and physical measurements of height and weight will be performed. Assessment of safety (adverse events, serious adverse events, laboratory parameters) will also be performed. Tanner stage will be conducted in female subjects to determine the need for pregnancy testing. Highly sensitive pregnancy test will be performed and confirmed negative before each administration of denosumab at all scheduled visits in all female subjects who are at Tanner Stage 2 or (higher) or have had menarche.

Study-specific assessments include laboratory assessments (25 [OH] vitamin D, [redacted], antidenosumab antibody), armspan, DXA (lumbar spine, proximal femur), x-rays (lateral thoracic, lumbar spine, anteroposterior knees), dental x-rays, oral visual inspection, and clinical fracture recording.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1.

Statistical Considerations

Statistical analysis in this study will be descriptive in nature and statistical inferences will be for guidance only. Descriptive statistics will be provided for baseline demographics and subject characteristics based on FAS, and for all endpoints based on their respective analysis sets and within each pattern of treatment received during the study if data warrant. Continuous outcomes will be summarized by the number of non-missing values, mean, SD, median, lower and upper quartiles and minimum and maximum values. Nominal and ordinal categorical variables will be summarized using counts and percentages.

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events,

adverse events leading to withdrawal from investigational product (denosumab), and adverse events of special interest will also be provided. The adverse events of special interest will include changes in growth plate morphology, severe or symptomatic hypocalcemia, osteonecrosis of the jaw (ONJ), abnormal molar eruption, hypercalcemia, and abnormal mandibular shaping.

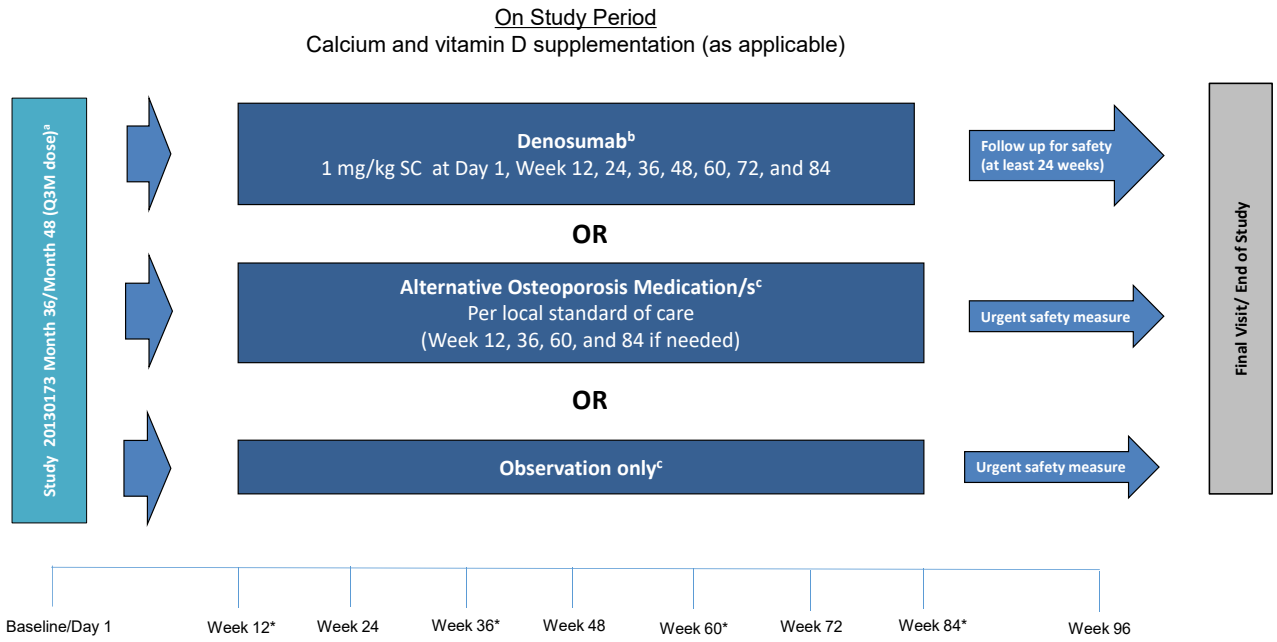
Details will be described in the Statistical Analysis Plan. For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



EOS = end of study; IP = investigational product; Q3M = 3-Month Dosing Regimen; SC = subcutaneous

[a] Subjects who decline Q3M dose change in Study 20130173 may also be offered participation in Study 20170534. All subjects already on study who consent to Q3M and have not had opportunity to complete 12 months of dosing will be allowed to continue until they have completed a minimum of 12 months (note: subjects may continue up to week 96 on Q3M).

[b] Following urgent safety measure, treatment with denosumab will be discontinued for all subjects and subjects will be followed for safety for 24 weeks following the last dose of denosumab. Subjects who were on denosumab (every 3 months or every 6 months treatment) and stopped denosumab more than 24 weeks ago should be scheduled for their EOS Visit at the next scheduled visit and have their EOS Visit assessments conducted per the current Schedule of Assessments.

[c] Subjects on alternative or observational therapy that have never taken denosumab should complete the EOS assessments at the next scheduled visit.

* Quarterly visits: These visits (week 12, 36, 60, 84) are only required for subjects receiving denosumab or if the subject is treated with alternative osteoporosis medication/s requiring quarterly administration. Observation-only subjects should attend every 6 months.

2.2 Schedule of Activities

Table 2-1. Schedule of Activities for Investigational Product (3-Month Dosing Regimen), Alternative Therapies, and Observation

PROCEDURE	Screening [a]	Treatment Period (24 Months)															Final Visit
		Day 1[b]	Day 10[c]	Day 30[c]	Week 12[d]	Day 10[c]	Day 30[c]	Week 24	Day 10[c]	Day 30[c]	Week 36[d]	Week 48	Week 60[d]	Week 72	Week 84[d]	Additional 12 weeks safety follow- up	Week 96/End of Study/ET
		Day visits have a ± 3 days window; week visits have a ± 7-day window															
GENERAL AND SAFETY ASSESSMENTS																	
Informed consent/assent	X																
Inclusion and exclusion criteria	X																
Demographics	X[e]																
Medical history	X[f]																
Physical examination[g]	X[h]				X			X			X	X	X	X	X	X	X
Tanner stage[i]	X[h]				X			X			X	X	X	X	X	X	X
Vital signs	X[h]				X			X			X	X	X	X	X	X	X
Adverse events[j]	X[k]	X	X	X	X			X			X	X	X	X	X	X	X
Concomitant medication[j]	X[f]	X[f]	X	X	X			X			X	X	X	X	X	X	X
LABORATORY ASSESSMENTS																	
Pregnancy test (urine dipstick method)[l]	X				X			X			X	X	X	X	X	X	X
Hematology	X[h]				X			X			X	X	X	X	X	X	X
Chemistry[c]	X[h,u]		X[u]	X[u]	X[u]	X[u,v]	X[u,v]	X[u]	X[u,v]	X[u,v]	X[u]	X[u]	X[u]	X[u]	X[u]	X	X[u]
Urine calcium[c]	X	X			X			X			X	X	X	X	X	X	X
25 OH) tam n D																	
[redacted]																	
Antidenosumab-antibody[n]	X[h]											X					X

Abbreviations and footnotes are at the end of the table.

Table 2-1. Schedule of Activities for Investigational Product (3-Month Dosing Regimen), Alternative Therapies, and Observation

PROCEDURE	Screening [a]	Treatment Period (24 Months)															Final Visit
		Day 1[b]	Day 10[c]	Day 30[c]	Week 12[d]	Day 10[c]	Day 30[c]	Week 24	Day 10[c]	Day 30[c]	Week 36[d]	Week 48	Week 60[d]	Week 72	Week 84[d]	Additional 12 weeks safety follow- up	Week 96/End of Study/ET
		Day visits have a ± 3 days window; week visits have a ± 7-day window															
STUDY-SPECIFIC ASSESSMENTS																	
Armspan	X[h]											X					X
DXA (AP lumbar spine)[o]	X[h]	X[m]						X				X					X
DXA (proximal femur – total hip and femoral neck in subjects ≥ 5 years of age)[o]	X[h]							X				X					X
X-ray (lateral thoracic, lumbar spine)[o]	X[h]											X					X
X-ray (AP knees)[n,o]	X[h]							X				X		X			X
Dental X-ray (cephalogram and panoramic radiograph)[o]	X[h]																X
Oral visual inspection	X	X			X			X			X	X	X	X	X	X	X
Dental X-ray (molars)[o,p]	X[p]																
Clinical fracture recording[q]		X	X	X	X			X			X	X	X	X	X	X	X
STUDY TREATMENTS																	
Investigational product (denosumab)[r]		X[s]			X			X			X	X	X	X	X		
Alternative osteoporosis medication/s[r]		Continuously, as per local standard of care															
Dispensation of calcium and vitamin D[t]		X			X			X			X	X	X	X	X	X	

AP = anteroposterior; [redacted] DXA = Dual-energy X-ray absorptiometry; EOS = end of study; ET = Early Termination; OI = osteogenesis imperfecta; [redacted]

[a] Screening and study day 1 may be combined and occur on the same day. Study day 1 should occur within 7 days from Screening.
[b] Screening should take place within 28 days of the Study 20130173 End of Study visit and may occur on the same day. Completion of screening assessment occurs on study day 1 of study, which can also be combined with Study 20130173 End of Study and screening visit. The 3-Month Dosing Regimen day 1 is defined as the date of reconsent/assent and the first dose of denosumab on the 3-Month Dosing Regimen. All subjects previously enrolled into the study prior to this amendment will be eligible to transition to the 3-Month Dosing Regimen. Study 20130173 subjects who do not consent/assent to transition to 3-Month Dosing Regimen will perform a 20130173 EOS prior to month 36 and be offered the opportunity to enroll into this study.
[C] The assessments on day 10 and day 30 after day 1 and weeks 12 and 24 are only required for subjects who started on 3-Month Dosing Regimen for the first time (± 3 days). Urine calcium is needed on day 1 only if it was not collected at Screening. Serum calcium to be performed on days 10 and 30 following week 12 and week 24 doses.
[d] Quarterly visits: These visits (week 12, 36, 60, and 84) are only required for subjects receiving denosumab or if the subject is treated with alternative osteoporosis medication/s requiring quarterly administration. If alternative medication is given more frequently than at the scheduled quarterly visits, the interim dosing only visits could be administered by any health care provider (refer to Section 5.1). Observation only subjects should attend every 6 months.
[e] Demographic data (except age) will be carried over from Study 20130173.
[f] Medical history: all medical history including fracture history and OI history will be transferred from Study 20130173 to Study 20170534. Resolved events (including fractures) on Study 20130173 should be entered in the appropriate medical history or subject fracture history forms at discretion of the investigator.
[g] Physical examination includes height and weight.
[h] Screening and study day 1 visit should coincide with Study 20130173 End of Study visit. These assessments are expected to be performed at Study 20130173 End of Study visit and should not be duplicated. All imaging and laboratory assessments should be conducted for Study 20130173 End of Study visit and data will be transferred to the Study 20170534 screening visit. Physical examination, physical measurements, vital signs, Tanner stage, and pregnancy test should be conducted if Study 20130173 End of Study and screening visits do not occur on the same day.
[i] Tanner stage to be conducted in female subjects to determine the need to perform a pregnancy urine dipstick test at these visits.
[j] Data collected at supplemental visits includes adverse events, serious adverse events, and concomitant medications.
[k] Ongoing events at screening and any new events since Study 20130173 End of Study visit will be entered into medical history.
[l] To be performed in all female subjects who are at Tanner Stage 2 or (higher) or have had menarche. Highly sensitive pregnancy test will be performed and confirmed negative before each administration of denosumab at all scheduled visits in all female subjects who are at Tanner Stage 2 or (higher) or have had menarche. Additional on-treatment pregnancy testing (urine) may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations. Pregnancy tests should be performed for subjects receiving alternative OI medications (alternative therapy includes the commercial denosumab 6-Month Dosing Regimen) as per label instructions.
[m] See Section 9.2.2. The DXA scan to be performed in duplicate at day 1. Only required for subjects going onto denosumab 3-Month dosing for the first time.
[n] Only for subjects who continue denosumab in this study. For X-ray (AP knees): Only in subjects with open growth plates who do not have bilateral hardware.
[o] All images/reports (as applicable) to be sent to the central imaging vendor. 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.
[p] To be performed only if a delay in molar eruption is suspected based on oral visual inspection (refer to Section 9.2.3.3; Oral Visual Inspection).
[q] An X-ray should be sent to the central imaging vendor for all non-vertebral fractures occurring after enrollment.
[r] Subjects will receive either denosumab 3-Month Dosing Regimen or alternative osteoporosis medication/s per local standard of care (including commercial denosumab at a 6-Month Dosing Regimen) or observation only (no intervention). Changes to study treatment will occur only at the next scheduled visit for that therapy, either denosumab 3-Month Dosing Regimen or alternative osteoporosis medication/s.
[s] Study day 1: up to a 7-day window is allowed for administration of first dose of Amgen investigational product (denosumab).
[t] Calcium and vitamin D are recommended for subjects receiving denosumab.
[u] At all study visits, signs and symptoms of hypocalcemia will be assessed and subjects reminded of importance of taking calcium and vitamin D.

[v] On days 10 and 30 following weeks 12 and 24, blood collection may be performed by a qualified individual at the subject's home, in lieu of a site visit.

3. Introduction

3.1 Study Rationale

Rationale for Stopping Denosumab Administration (Protocol Amendment 4)

Recently, life-threatening events of hypercalcemia were reported on denosumab 1 mg/kg Q3M regimen in the pediatric OI subjects in Study 20130173. 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.

As a result of the potentially life-threatening risk of hypercalcemia, starting from 30 September 2021, all further dosing of denosumab in this study was stopped and enrollment was closed. Refer to Section 5.1.

Study 20170534 **was** an open-label extension of Study 20130173 to assess long-term safety and efficacy of current or prior treatment with denosumab in children/young adults with osteogenesis imperfecta (OI). This study **was** required for compliance with key binding elements from the denosumab Pediatric Investigational Plan (PIP) for Study 20130173 whereby subjects **were** offered participation in a long-term open-label follow-up study.

3.2 Background

3.2.1 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 25000 live births (Byers, 2000).

At least 12 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 have had 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.

3.2.2 Amgen Investigational Product Background: Denosumab

Denosumab is a fully human monoclonal antibody that binds with high affinity (dissociation equilibrium constant [Kd] 3 x 10^{-12} M) and specificity to receptor activator of nuclear factor kappa-B ligand (RANKL) and neutralizes the activity of RANKL, preventing activation of its receptor, receptor activator of nuclear factor kappa-B (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 pharmacokinetics (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, and treatment of bone

loss in women receiving aromatase inhibitor therapy for breast cancer, and treatment of adult glucocorticoid-induced osteoporosis.

A detailed description of the chemistry, pharmacology, efficacy, and safety of denosumab is provided in the Denosumab Investigator's Brochure.

3.2.3 Alternative Osteoporosis Medication/s Product Background

Initiation, selection, and dosing regimen of alternative osteoporosis medication/s including reduced dosing in subjects who discontinued denosumab prior to or upon entering study or who discontinue denosumab during the study is at investigator discretion, per local standard of care. Refer to the regional manufacturer package insert for additional information.

3.3 Benefit/Risk Assessment

This pediatric study involves greater than minimal risk in part due to the increased skeletal growth in this population. OI is clinically associated with osteoporosis and fragility fractures, which may benefit from antiresorptives such as bisphosphonates or denosumab. Use of denosumab in this population may present the prospect of direct benefit to the subject. Pediatric subjects treated with denosumab in this study are expected to have a risk profile comparable to that observed in adults. 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. The potential benefit:risk assessment will be established in Study 20130173 and this study. Several aspects will be investigated and are further considered in Section 9. Additional information on specific risks in this pediatric population for patients on denosumab are provided below and in Section 3.3.3.1 to Section 3.3.3.8.

Preliminary study data indicate that after administration of 1 mg/kg denosumab, PK exposures are cleared within 3 months and [redacted] 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 in the 20130173 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.

Refer to the Denosumab Investigator's Brochure for further data on denosumab.

3.3.1 Therapeutic Context

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); men with osteoporosis (Study 20080098), and adult subjects with glucocorticoid-induced osteoporosis (GiOP) (Study 20101217), as well as ongoing studies in pediatric subjects with OI (Study 20130173) and GiOP (Study 20140444).

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).

3.3.2 Key Benefits

The clinical benefits of denosumab treatment derive from its inhibition of RANKL binding to RANK, thereby inhibiting the formation, activation, and survival of osteoclasts, decreasing bone resorption, and increasing bone mass, volume, and strength (Brunetti et al, 2016; Kostenuik, 2005). In children with OI, denosumab may have provided benefit due to its unique mechanism of action, reversible PK, and ease of administration (subcutaneous [SC] injection). Given the life-threatening events of hypercalcemia reported in the 20130173 study, the hypercalcemia was identified as 'important identified risk' of denosumab (Prolia) use in pediatric OI studies, and the benefit-risk profile of denosumab in the OI population is not considered positive.

3.3.3 Key Risks

Key risks with denosumab in adult indications include hypocalcemia, hypercalcemia, osteopetrosis, tooth eruption, multiple vertebral fractures following discontinuation of denosumab treatment, osteonecrosis of the jaw (ONJ), and atypical femoral fracture (AFF), as detailed in Section 3.3.3.2 to Section 3.3.3.8.

3.3.3.1 Risks

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. 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; ONJ, 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 extremities, and musculoskeletal pain. Multiple vertebral fractures and hypercalcemia (in subjects with growing skeletons) may occur following discontinuation of denosumab treatment. Additionally, hypercalcemia following denosumab discontinuation is an important potential risk in patients with growing skeletons. There is a possibility that hypercalcemia could occur at the end of the dosing interval when a subject is still receiving Investigational Product.

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.

In the combined Q3M/Q6M dosing cohorts, treatment-emergent adverse events of hypocalcemia have been reported in 19 (12%) of study subjects. There have been no serious adverse events of hypocalcemia reported. There have been no cases of positively-adjudicated osteonecrosis of the jaw.

In a substudy assessment of urine calcium, DPD/creat ratio, and NTX for each treatment cycle shows the following trends:

- Urine calcium/creatine ratio declines in first 2 weeks following investigational product administration and increases to slightly above baseline in weeks 12-18
- Absolute value and DPD/creatine 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 investigational product administration
- Urine N-telopeptide (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.

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).

3.3.3.2 Hypocalcemia

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

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

- Calcium and vitamin D supplementation will be given to all subjects receiving study medication (denosumab)
- 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 (denosumab) and institution of appropriate medical treatment

3.3.3.3 Hypercalcemia

The higher bone turnover rates expected at baseline in children with OI may increase the risk for rebound hypercalcemia in the latter part of the dosing interval due to release of bone turnover inhibition. In addition, 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 (Grasemann et al, 2013; Boyce et al, 2012).

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

- If a subject becomes hypercalcemic during the course of denosumab treatment, the calcium and/or vitamin D supplementation may be discontinued or dose adjusted at site discretion until the serum or urine calcium concentration has returned to the normal range
- Serum and urine calcium will be measured routinely during 3-Month Dosing Regimen visits

As of 07 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.

Therefore, hypercalcemia is a risk in this pediatric population receiving denosumab.

Starting from 30 September 2021, due to the life-threatening events of hypercalcemia reported on denosumab use in the pediatric OI study, subjects will not receive any further dosing on 20170534 and will be followed for safety for 24 weeks following the last dose of denosumab.

3.3.3.4 Osteopetrosis

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

Strategies to assess changes to the skeleton include the following:

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

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

3.3.3.5 Tooth Eruption

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

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

- Molar eruption and mandibular shaping will be monitored using visual inspection and X-ray assessments

3.3.3.6 Multiple Vertebral Fractures Following Treatment Discontinuation

Multiple vertebral fractures may occur following discontinuation of denosumab treatment, particularly in adult subjects with a history of vertebral fracture. Among postmenopausal women with osteoporosis who discontinued denosumab during the placebo-controlled Study 20030216 and its open-label active-treatment extension, the incidence of new vertebral fracture was higher than in subjects who remained on-treatment, but similar to the incidence in subjects who discontinued placebo, ie, had never been treated. Among subjects who experienced off-treatment new vertebral fractures, a greater percentage of those who discontinued denosumab than placebo sustained multiple new vertebral fractures. Prior vertebral fracture before or during treatment was the strongest predictor of off-treatment new vertebral fracture, including multiple vertebral fractures.

During the 24-month study period, subjects may discontinue denosumab as study treatment at investigator discretion and either be treated with an alternative osteoporosis medication/s of investigator's choice administered per local standard of care or followed on observation only (no intervention).

Given the identified risk for multiple vertebral fractures after denosumab cessation in study subjects at high risk for fracture, subjects who stop denosumab during the study or at the end of the study, and are judged by the investigator to be at high risk of multiple vertebral fractures following treatment discontinuation, should be considered for transition to an alternative osteoporosis medication/s per local standard of care.

It is recognized that (with the exception of neridronate in Italy), no medications are approved for the treatment of pediatric OI, and antiresorptive use is considered off-label; however, local standard of care for pediatric subjects with OI may include bisphosphonate use. Therefore, the decision to use an alternative osteoporosis medication/s and selection of the dose and regimen will be at investigator discretion.

3.3.3.7 Osteonecrosis of the Jaw Events

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 (including after molar eruption) and x-ray assessments when indicated

3.3.3.8 Atypical Femoral Fracture Events

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, 2008; 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 (Nicolau 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 6 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 terminology, all femur fractures will be reviewed as typical OI femur fractures (TOIFF).

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate long-term safety of denosumab in subjects with pediatric osteogenesis imperfecta (OI) completing Study 20130173	• The primary endpoints are subject incidence of adverse events, serious adverse events, and adverse events of special interest, subject incidence of antidenosumab antibodies, changes from baseline in laboratory values and vital signs, and subject incidence of metaphyseal index Z-score above age-appropriate normal range, abnormal molar eruption, and mandibular shaping
Secondary	
• To describe changes in bone mineral density (BMD) of lumbar spine and proximal femur (total hip and femoral neck) from baseline to **6,** 12**, and 24** months	• Actual values and changes in BMD Z-score of lumbar spine and proximal femur (total hip and femoral neck) from Study 20170534 baseline, as assessed by dual X-ray absorptiometry (DXA), at **6,** 12**, and 24** months

Exploratory
[redacted]

[redacted]

Rationale for Changing Study Endpoints (Protocol Amendment 5)

Fracture and growth velocity efficacy endpoints have been deleted due to multiple treatment sequences during the trial and an urgent safety measure with early termination leading to a small number of subjects for quality statistical analysis. Adverse events of fracture, including femur fractures, will be presented in the adverse event tables.

4.2 Hypotheses

This study is descriptive in nature and does not involve testing formal hypotheses.

5. Study Design

5.1 Overall Design

Starting from 30 September 2021, due to the life-threatening events of hypercalcemia reported on denosumab use in the pediatric OI study, **it was decided that** subjects **would** not receive any further dosing on 20170534 and **would** be followed for safety for 24 weeks following the last dose of denosumab (see Section 5.1.1). Study 20170534 **was** an open-label, prospective, extension study of Study 20130173 to assess long-term safety and efficacy of current or prior treatment with denosumab in children/young adults with OI. This study **was** required for compliance with key binding elements from the denosumab PIP for Study 20130173. All subjects who complete**d** EOS on Study 20130173, regardless of whether they received investigational product until the last protocol-specified dose on the 20130173 study or ended investigational product early, **were** offered participation in a long-term open-label follow-up study – where this protocol ha**d** been approved at the site. Subjects who withdr**ew** consent/assent to transition to 3-Month Dosing Regimen on 20130173 **were** also offered participation in this study. When subjects in Study 20130173 near**ed** the EOS visit (completion), subjects **were** offered participation in Study 20170534. If a subject **was** rolled over into the 20170534 study, they **were** offered to receive alternative treatment including commercial denosumab every 6 months (6-Month Dosing Regimen) or **would** be observed without any treatment or the investigational product given every 3 months (3-Month Dosing Regimen).

For subjects that consent/assent to participate in Study 20170534, Screening and study day 1 visit should coincide with Study 20130173 EOS visit. Where this is not possible,

the screening visit should occur on or within 28 days of the Study 20130173 EOS visit. Study day 1 should occur within 7 days from Screening.

Subjects enrolled in the study may be treated with denosumab or alternative osteoporosis medication/s at the discretion of the investigator, or may discontinue any osteoporosis medication for off-treatment observation. At any time during the study subjects may (1) discontinue denosumab, (2) resume denosumab (3-Month Dosing Regimen), (3) initiate alternative osteoporosis medication/s, and (4) discontinue alternative osteoporosis medication/s, based on the medical judgment of the investigator and per local standard of care (as applicable). In subjects who transition from denosumab to an alternative osteoporosis medication, the latter should be administered approximately 3 months after the last denosumab dose, ie, the next visit scheduled to receive study treatment, unless otherwise medically indicated. Similarly, transition from 1 standard of care osteoporosis medication to another or a reduced dose of denosumab should occur at the end of the dosing interval of the previous therapy. For subjects electing alternative therapy, alternative therapy may be administered by any qualified healthcare provider (HCP). The HCP must provide a written note to the subject describing the nature and date of alternative treatment to be documented by the investigative site. Subjects on alternative regimens given by HCPs other than investigational product, will continue to attend the study site every 6 months (weeks 12, 36, 60, and 84).

Subjects should return to the study site every 12 weeks (± 7 days) for treatment with denosumab. Subjects who are on observation only or on 6-Month dosing for alternative medications may attend scheduled visits every 24 weeks. For subjects receiving alternative osteoporosis medication/s, dosing frequency will be determined by the treatment regimen selected by the investigator, subjects will attend scheduled study visits every 6 months as per the Schedule of Activities (Table 2-1). In this case, where a dosing visit does not coincide with a scheduled study visit, additional collection of assessments is not required other than recording of the medication on the concomitant medication eCRF page under alternative osteoporosis medication. All subjects should return for a final EOS/Early Termination visit.

Samples will be collected for clinical laboratory testing, including assessment of BTM and antidenosumab antibodies. Adverse events will be assessed throughout the study. Subjects will undergo DXA and radiographic assessments as detailed in the Schedule of Activities (Table 2-1).

The overall study design is described by a study schema in Figure 2.1. The endpoints are defined in Section 4.1.

5.1.1 All Dosing Stopped and Subjects on Denosumab Followed for Safety

Recently, life-threatening events of hypercalcemia were reported on denosumab 1 mg/kg Q3M regimen in the pediatric OI subjects within 20130173 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 and decided to stop the 20170543 study for any further enrollment or dosing with denosumab.

Per the 30 September 2021 DIL, all investigators were notified to immediately stop denosumab treatment and continue the study as per the normal schedule of assessments (without denosumab treatment). All subjects participating in the study will be followed for 24 weeks after their last dose of denosumab. At 24 weeks the End of Study (EOS) Assessments should be completed per the current Schedule of Activities (Table 2-1).

Subjects who were on denosumab (every 3 months or every 6 months treatment) and stopped denosumab more than 24 weeks ago should be scheduled for their EOS Visit at the next scheduled visit and have their EOS Visit assessments conducted per the current Schedule of Activities (Table 2-1).

Subjects on observational or alternative therapies that have never taken denosumab should complete their EOS visit at the next scheduled visit (Table 2-1).

5.2 Number of Subjects

The number of subjects in this study will be determined by the number of subjects completing Study 20130173, and who are willing and able to participate in the long-term follow-up study.

Subjects in this clinical investigation shall be referred to as “subjects.” For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced. Subjects may switch to an alternative osteoporosis medication/s, or, if they discontinue all treatment, they will be followed as off-treatment (observation only). Subjects may resume/start denosumab 3-Month Dosing Regimen at any time during the study. Any subject starting denosumab 3-Month Dosing Regimen for the first time will complete day 1 and continue for a minimum of 12 months.

5.2.2 Number of Sites

Approximately 40 investigative sites in North America, Europe, and Australia were planned in Study 20130173. Any sites with subjects willing and able to participate in this study will be included. Sites that do not enroll any subjects within 28 days of the last participant last visit of Study 20130173 will be closed as subjects would no longer be eligible for inclusion. Subjects who were already taking denosumab 6-Month Dosing Regimen will be offered the opportunity to move to the 3-Month Dosing Regimen.

5.3 End of Study

5.3.1 End of Study Definition

An individual subject is considered to have completed the study if he/she has completed week 96 visit, except for those subjects enrolled prior to the 6-Month Dosing Regimen of Protocol Amendment 1 and transitioning to a 3-Month Dosing Regimen. Starting from 30 September 2021, subjects on denosumab who had not completed their EOS were immediately discontinued from denosumab and will be followed for 24 weeks following the last dose of denosumab.

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

5.3.2 Study Duration for Subjects

The duration of study for each subject that enrolls in this study is expected to be up to 120 weeks, including treatment and final visit/EOS visit, whether or not they are receiving denosumab or alternative osteoporosis medication or off-treatment (observation only). For subjects already enrolled on the 20170534 study on the 6-Month Dosing Regimen, regardless of the arm of the study they are on, that consents/assents/switches to denosumab investigational product 3-Month Dosing Regimen (for the first time) whom are expected to complete a minimum of 12 months on investigational product, may consequently exceed the expected 96 weeks on-study if they switch beyond week 48.

5.4 Justification for Investigational Product Dose

Ongoing bone treatment will be at the discretion of the investigator, allowing denosumab, alternative osteoporosis medication/s per local standard of care, or off-treatment observation. Subjects who continue denosumab on 3-Month Dosing Regimen from 20130173 will continue the dose (1 mg/kg, up to a maximum of 60 mg) used in Study 20130173, with appropriate adjustments made for change in body weight.

Dose and dosing regimen for alternative osteoporosis medication/s that may be used during the study at investigator's discretion will be determined by local standard of care.

5.5 Patient Input on Study Design

Not applicable.

6. Study Population

Eligibility will be evaluated at EOS visit of Study 20130173 based on assessments done at this visit including discussion with subject and willingness to participate within 28 days. Screening will occur on or within 28 days of the EOS visit of Study 20130173.

Before any study-specific activities/procedures, the appropriate written informed consent/assent must be obtained (see Section 12.3).

Subjects who were enrolled into this study under Protocol Amendment 1 will be reconsented/reassented at their next visit, and those receiving investigational product (denosumab) will transition to a 3-Month Dosing Regimen. Subjects receiving alternative OI medication/s (alternative therapy includes the commercial denosumab 6-Month Dosing Regimen) or off-treatment (observation only) may also consent/assent to resume denosumab 3-Month Dosing Regimen. Subject eligibility will not be re-assessed at time of transition to 3-Month Dosing Regimen.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

6.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101. Subject has provided informed consent/assent prior to initiation of any Study 20170534 specific activities/procedures.

     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. Subject was enrolled in Study 20130173 and**:**

     - completed the 20130173 EOS visit (regardless of completing or ending investigational product early).

     OR

     - Subjects who do not reconsent/reassent to transition to 3-Month Dosing Regimen on Study 20130173 are also eligible for enrollment

     OR

- Early terminated from Study 20130173 as a result of meeting BMD Z-score investigational product stopping criteria and was required to early terminate from the study

6.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Prior/Concomitant Therapy

201. Treatment with any prohibited proscribed medications (see Section 7.1.7) while receiving denosumab. Eligibility into study treatment with alternative osteoporosis medication/s of investigator's choice, follow guidelines per the specific alternative osteoporosis medication/s selected. For subjects off-treatment (observation only), no prohibited medications apply.

Prior/Concurrent Clinical Study Experience

202. Subjects currently receiving treatment in another investigational device or drug study other than Study 20130173. Other investigational procedures while participating in this study are excluded.

Other Exclusions

203. For subjects expected to receive investigational product (denosumab) at study day 1: Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 5 months after the last dose of denosumab. Females of childbearing potential (Tanner Stage ≥ 2) should only be included in the study after a negative highly sensitive urine pregnancy test. For study treatment with alternative osteoporosis medication/s of investigator's choice, follow guidelines per the specific alternative osteoporosis medication/s selected. For subjects off-treatment (observation only), no exclusion applies.

204. For subjects expected to receive investigational product (denosumab) at study day 1: Female subjects of childbearing potential unwilling to practice true sexual abstinence (refrain from heterosexual intercourse) or use 1 highly effective method of contraception during treatment and for an additional 5 months after the last dose of investigational product (denosumab). For study treatment with alternative osteoporosis medication/s of investigator's choice, follow contraception guidelines per the specific alternative osteoporosis medication/s selected. For subjects off-treatment (observation only), no contraception required. Refer to Section 12.5 for additional contraceptive information.

205. History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

6.3 Subject Enrollment

Due to the life-threatening risk of hypercalcemia, an urgent safety measure has been implemented to stop all enrollment and treatment with denosumab with the EOS visit 24 weeks after the last dose of denosumab. See Section 5.1.1.

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/assent form, and all other subject information, if applicable (see Section 12.3).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent/assent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides 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) and contact the Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) to enroll the subject.

Each subject who signs the IRB/IEC-approved ICF will be assigned the same subject identification number as the parent study (Study 20130173) before any study-related activities/procedures are performed.

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.

Subjects enrolled prior to this Protocol Amendment will be reconsented/reassented. Subject eligibility will not be re-assessed at time of transition to 3-Month Dosing Regimen.

- Subjects who do not reconsent/assent to a 3-Month Dosing Regimen will be discontinued from investigational product (denosumab) but may switch to alternative OI medication or off-treatment (observation only).
- Subjects previously receiving alternative OI medication/s or off-treatment (observation only) may resume investigational product (denosumab) 3-Month Dosing Regimen.

A subject call will be placed in the IVRS/IWRS at time of reconsent/assent 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.

6.4 Screen Failures

The investigator will maintain a Screening and Enrollment log to document all eligible subjects from parent Study 20130173, that includes limited information about the potential candidate, such as date of informed consent/assent (if obtained) and screen fail reason.

7. Treatments

There is no protocol-required investigational product in this trial. All treatment is at investigator discretion and not mandated by the protocol. Subjects may continue to be treated with open-label denosumab at a 3-Month Dosing Regimen, which for the purposes of this study is defined as any investigational product. Investigator may decide to treat with alternative osteoporosis medication/s or observation only (no intervention) rather than administer investigational product. All subjects regardless of treatment with investigational product, alternative osteoporosis medication/s (denosumab at a 6-Month Dosing Regimen) or observation only (no intervention) may participate in this study.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of denosumab shown in Table 7-1 below.

7.1 Treatment Procedures

7.1.1 Investigational Products

Table 7-1. Study Treatments

Study Treatment Name	Amgen Investigational Product: Denosumab[a]
Dosage Formulation	70 mg/mL solution containing 1.7 mL in a 3 mL vial
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	1 mg/kg body weight not to exceed 60 mg per subject at any visit day 1, at week 12, week 24, week 36, week 48, week 60, week 72, and week 84
Route of Administration	SC injection
Accountability	The lot number(s), start date, start time, administration setting (in-clinic, non-clinic), total dose administered (quantity administered, and total administered) of investigational product are to be recorded on each subject's CRF.
Dosing Instructions	All SC injections must be administered by authorized site personnel. The denosumab SC injection must be administered as the last procedure after all other study visit procedures have been completed.

CRF = case report form; SC = subcutaneous

[a] Denosumab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

7.1.2 Non-investigational Products

Not applicable.

7.1.3 Medical Devices

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

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

7.1.4 Other Protocol-required Therapies

On the 3-Month Dosing Regimen, calcium and vitamin D were dispensed as a protocol-required therapy. For subjects on alternative therapies including the 6 Month Dosing Regimen, calcium and vitamin D were not protocol-required therapies and used at the investigator's discretion and local standard of care in pediatric OI. After the Urgent Safety Measure, all subjects are on alternative therapy with the exclusion of the 6 Month Dosing Regimen and are to use calcium and vitamin D at the site's discretion, and consistent with the local standard of care.

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

Subjects administered investigational product (denosumab) are recommended to take daily supplements of 30 to 50 mg/kg and not to exceed 1000 mg elemental calcium and at least 800 IU vitamin D while on denosumab during the study. Dose and duration of daily calcium and vitamin D supplementation when subjects are administered alternative osteoporosis medication/s will be determined by the investigator, per local standard of care.

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.

Any vitamin D and calcium dose adjustments will be recorded on the CRF Concomitant Medication page.

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

Additional details regarding these protocol-required therapies are provided in the IPIM.

7.1.5 Other Treatment Procedures

Not applicable.

7.1.6 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(s) associated with products described above and supplied by Amgen are to be reported according to the instructions provided in the modular IPIM.

7.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

All medications listed in the exclusion criteria, shown in Table 7-2 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. Bisphosphonates or other osteoporosis medications listed below are allowed as alternative osteoporosis medication/s, at the investigators discretion, for the duration of the study.

Table 7-2. List of Proscribed Therapy

Aluminum compounds used as phosphate binders	Chronic heparin use (> 7 days) (low molecular weight heparin [LMWH] are permitted)	Progestins, when used as monotherapy, including progestogens, pregnen(4) derivatives, and pregnadien derivatives (progestin monotherapy contraceptions are permitted)
Androgens[a]/Anabolic steroids: Natural or synthetic androgens alone or in combination with	Cinacalcet	

progestogen and/or estrogen including androstan derivatives, estren derivatives, 3-oxoandrosten(4) derivatives, and 5-androstandon derivatives		
Anticonvulsants not on stable dose and with difficulty regulation calcium and vitamin D: Antiepileptics, barbiturates and derivatives, hydantoin derivatives, oxazolidine derivatives, succinimide derivatives, carboxamide derivatives, and valproic acid (gabapentin and benzodiazepines are allowed)	Citrated products	Protease inhibitors
Any investigational agents for bone loss other than study drug	Fluoride	Strontium
Aromatase inhibitors: Including aminoglutethimide, anastrazole, exemestane, fadrozole, formestane, letrozole, roglemtimide, and vorozole	Gonadotropin-releasing hormone agonists	
Biologics: including biological (monoclonal antibody) immunosuppressives and antineoplastic agents (insulins and vaccines are allowed)	Growth hormone (unless stable for at least 3 months prior to screening)	
Calcitonin	Non-biologic immunosuppressants: Including chloroquine, hydroxychloroquine, azathioprine, leflunamide, sulfasalazine, cyclophosphamide, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, everolimus, and gold preparations	Tibolone
Calcium chelators	Lithium	
Chemotherapeutics	Parathyroid hormone (or a derivative), including semparatide, abaloparatide, and teriparatide	

[a] Androgen replacement therapy is not excluded.

7.2 Method of Treatment Assignment

Subjects who meet eligibility criteria will be administered treatment at investigator discretion and not mandated by the protocol. Subjects may continue to be treated with investigational product (denosumab) or alternative osteoporosis medication/s at the

discretion of the investigator, or may discontinue any osteoporosis medication for off-treatment observation.

The treatment administration date is to be documented in the subject's medical record and on the CRF.

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

7.4 Dose Modification

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 investigational product (denosumab).

Alternative osteoporosis medication/s selected will be adjusted per standard of care and local guidelines.

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

7.4.1.1 Amgen Investigational Product: Denosumab

Denosumab will be administered as a weight-based dose determined based on subject's weight assessed at the time of dosing every 3 months. There, dose reduction of denosumab is allowed. If a subject misses a scheduled dose of denosumab during a study visit, then he/she should return to the clinic to receive the missed dose within the visit window allowed for that particular visit. The clinical monitor should be contacted for specific instructions if a subject cannot receive his/her dose within the allowed window.

Subjects who discontinue denosumab may continue on-study on an alternative osteoporosis medication/s of investigator's choice or observation only (no intervention). Dosing with alternative osteoporosis medication should not be until the next scheduled dose (ie, 12 weeks from last dose of denosumab).

Subjects may discontinue alternative osteoporosis medication at any time. Subjects who discontinue from alternative osteoporosis medication may commence or re-start treatment with denosumab at the next scheduled study visit.

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.

See Section 12.7 for details on hepatotoxicity.

Administration of Amgen investigational product (denosumab) must be stopped for subjects in the following situations (in addition to reasons specified in Section 8.1). Subjects may continue on-study with alternative osteoporosis medication of investigator's choice or observation only (no intervention):

1. Severe or symptomatic hypocalcemia

   a 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
2. Severe or symptomatic hypercalcemia, which requires the use of a rescue medication for management
3. Osteonecrosis of the jaw
4. 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 (see above for guidance on restarting denosumab).
5. 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)
6. Decline in BMD Z-score by 0.5 units at any 6-month assessment compared to the 3-Month baseline

   a. Subjects who are removed from treatment as a result of the above fracture thresholds or lumbar spine BMD Z-score decline (3, 4, and 5) should be followed up and treated, if applicable, according to local standard of care, at the discretion of the treating physician
7. Changes in growth plate morphology, as observed in the 12-month monitoring, considered by the investigator to be unexpected and having an adverse clinical impact for the subject consistent with local institutional guidelines
8. Pregnancy
9. Severe hypersensitivity

7.4.1.2 Non-Amgen Non-Investigational Product(s): Alternative Osteoporosis Medication/s

The reason for dose change or change in alternative osteoporosis medication/s is to be recorded on each subject's CRF (Concomitant Medications Form). Dose changes are at the discretion of the investigator. Alternative osteoporosis medication/s is reviewed if any of the above situations occur, and changes or cessation will be at investigator discretion consistent with local standard of care.

7.4.1.3 Additional Safety Monitoring of Hypocalcemia

Hypocalcemia will be monitored as indicated in the Schedule of Activities (Table 2-1) to ensure the subject is not experiencing signs and symptoms of hypocalcemia.

7.4.2 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 12.7 for details regarding drug-induced liver injury (DILI) guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the Amgen investigational product (denosumab) during the study are provided in the IPIM.

7.6 Treatment Compliance

Not applicable for this study.

7.7 Treatment of Overdose

Overdose with this product (denosumab) has not been reported. The highest dose tested in clinical trials is 210 mg SC once every 6 months (6-Month Dosing Regimen). It is possible that an overdose may result in hypocalcemia.

Hypocalcemia, if severe, should be managed by oral or parenteral calcium replacement, as clinically indicated.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

All concomitant medications ongoing at the time of informed consent/assent will be recorded on the concomitant medications CRF.

7.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7.

Concomitant therapies are to be collected and entered on the CRF from signing of informed consent/assent through week 96 or EOS.

8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product (denosumab), and/or other protocol-required therapies, protocol procedures, or the study as a whole at any

time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product (denosumab), device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

The investigator and/or sponsor must decide to withdraw a subject(s) from investigational product (denosumab) for any of the following:

- Adverse event as defined in Section 7.4.1.1
- Pregnancy

The investigator may discontinue any alternative osteoporosis medication/s at any time based on clinical judgment.

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product (denosumab), and/or other protocol-required therapies, alternative OI medications, 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 study treatment or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 2-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have been discontinued from investigational product (denosumab) as a result of the urgent safety measure, and subjects who have previously discontinued IP and/or other protocol-required therapies, alternative OI medications, or procedures should not be automatically removed from the study. Subjects may continue to off-treatment (observation only) at investigator's discretion. 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 and can use alternative osteoporosis medication/s or be followed off-treatment (observation only) at investigator discretion. Following implementation of the Urgent Safety Measure, subjects who were receiving denosumab will be followed for 24 weeks for safety following the last dose of denosumab.

Subjects on observational or alternative therapies that have never taken denosumab should complete their EOS visit at the next scheduled visit (Table 2-1).

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event (including ONJ, and severe or symptomatic hypocalcemia; see Section 7.4.1.1)
- Subject request
- Pregnancy

Reasons for removal from alternative osteoporosis medication/s is at investigator discretion consistent with local standard of care.

8.2 Discontinuation From the Study

Withdrawal of consent/assent 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/assent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent/assent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product (denosumab) and/or procedures at any time during the study, but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product (denosumab) and must discuss with the subject the options for continuation of the Schedule of Activities (Table 2-1) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Activities (Table 2-1) 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, or from review of the medical records).

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 12.6 for further details). Refer to the Schedule of Activities (Table 2-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Washout, Run-in or Invasive Procedures

Not applicable for this study.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

8.3 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. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Table 2-1), is essential and required for study conduct.

9.1 General Study Periods

9.1.1 Screening and Enrollment

Informed consent/assent must be obtained before completing any study procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent/assent form, the site will register the subject in the IVRS/IWRS. Screening and study day 1 visit should coincide with Study 20130173 EOS visit, however if not, subjects should screen within 28 days from the Study 20130173 EOS visit. Study day 1 should occur within 7 days from Screening.

Data from Study 20130173 EOS visit will be used as baseline and assessments should not be duplicated. All imaging and laboratory assessments should be conducted for Study 20130173 EOS visit and data will be transferred to the Study 20170534 screening visit. Physical examination, physical measurements, vital signs, Tanner stage, and pregnancy test assessments should be conducted if Study 20130173 EOS and screening visits do not occur on the same day. 25 (OH) vitamin levels should be collected at Screening.

The investigator will maintain a Screening and Enrollment log to document that all eligible subjects were offered participation. The investigator should note the subject number, enrollment date, or reason that the subject screen failed or did not enroll.

9.1.2 Treatment Period

As a result of the potentially life-threatening risk of hypercalcemia, starting from 30 September 2021, all further dosing of denosumab in this study was stopped and enrollment was closed. Refer to Section 5.1.

Visits will occur per the Schedule of Activities (Table 2-1). On-study visits may be completed within ± 7 days. Study day 1 is the date of the first dose of investigational

product (denosumab) or alternative osteoporosis medication/s, or the date of informed consent/assent for observation only subjects. All subsequent doses and study visits will be scheduled based on the Study day 1 date. Administration of investigational product (denosumab) or alternative osteoporosis medication is to be administered by authorized site personnel only after all other study visit procedures have been completed.

If the investigator has opted for No Study Treatment (observation only) for the subject, all study assessments will be performed as per the Schedule of Activities (Table 2-1).

Subjects enrolled prior to this Protocol Amendment and receiving 6-Month Dosing Regimen will be reconsented/assented to the 3-Month Dosing Regimen. Subjects will complete a Study day 1 assessments for 3-Month Dosing Regimen per Schedule of Activities (Table 2-1).

Subjects who do not consent/assent to 3-Month Dosing Regimen may switch to an Alternative OI Medication/s or off-treatment (observation only). Subjects may resume investigational product (denosumab 3-Month Dosing Regimen) at any time.

9.1.3 Safety Follow-up/End of Study

Per the 30 September 2021 DIL, all investigators were notified to immediately stop denosumab treatment and continue the study as per the normal schedule of assessments (without denosumab treatment). All subjects participating in the study will be followed for 24 weeks after their last dose of denosumab. At 24 weeks the End of Study (EOS) Assessments should be completed per the current Schedule of Activities (Table 2-1).

Subjects who were on denosumab (3 months or every 6 months treatment) and stopped denosumab more than 24 weeks ago should be scheduled for their EOS Visit at the next scheduled visit and have their EOS Visit assessments conducted per the current Schedule of Activities (Table 2-1).

Subjects on alternative or observational therapy that have never taken denosumab should complete the EOS assessments at the next scheduled visit (Table 2-1).

If possible, the procedures of the EOS visit should be completed at the time of withdrawal with the following exception:

- Procedures involving X-ray radiation exposure other than DXA assessment may not be performed if < 3 months have elapsed since the previous radiographic assessment.
    - DXA scans will only be performed if > 30 days have elapsed since the previous assessment.

9.1.4 End of Study

The EOS visit will be performed during the safety follow-up as described in Section 9.1.3.

9.2 Description of General Study Assessments and Procedures

As a result of the potentially life-threatening risk of hypercalcemia, starting from 30 September 2021, all further dosing of denosumab in this study was stopped and enrollment was closed. Refer to Section 5.1.

The sections below provide a description of the individual study procedures for required time points.

9.2.1 General Assessments

9.2.1.1 Informed Consent/Assent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent/assent before any study-specific procedures are performed.

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.

9.2.1.2 Demographics

Demographic data (except age) will be carried over from Study 20130173. Demographic data collection, including sex, age, race, and ethnicity may be used to study their possible association with subject safety and treatment effectiveness.

9.2.1.3 Medical History

All data entered in the 20130173 medical history, fracture history, and OI history will be transferred into the 20170534 database. Resolved and ongoing adverse events (including fractures) on Study 20130173 will be entered into the medical history or subject fracture history forms at the investigator discretion.

Events starting after the EOS visit of Study 20130173 but prior to the screening visit of this study will be entered in the Event CRF and flagged as adverse events occurring between last study visit of Study 20130173 and prior to informed consent/assent on Study 20170534.

9.2.1.4 Physical Examination

A pelvic, breast, or rectal examination is not required unless a specific evaluation is warranted. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

Where the screening visit coincides with the Study 20130173 EOS visit, the physical examination should not be repeated. The physical examination should be conducted if the Study 20130173 EOS and screening visits do not occur on the same day.

9.2.1.5 Physical Measurements

Height in centimeters should be measured without shoes. Height measurements 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.

Weight in kilograms should be measured without shoes.

Armspan 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.

Where the screening visit coincides with the Study 20130173 EOS visit, physical measurements should not be repeated. Physical measurements should be assessed if the Study 20130173 EOS and screening visits do not occur on the same day.

9.2.2 Efficacy Assessments

Radiographic Assessments

Radiographic assessments should be conducted for the Study 20130173 EOS visit and data will be transferred to the Study 20170534 screening visit.

All available radiographic assessments for evaluation of potential fracture from day 1 until EOS, including any unscheduled assessments, will be submitted to central imaging vendor for final analysis.

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 Table 2-1. Scans will be performed at all applicable visits.

A DXA should be performed as indicated in the Schedule of Activities (Section 2.2).

Only General Electric Lunar or Hologic bone densitometers will be allowed for this study. The same DXA machine should 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.

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 annually to determine vertebral fracture status.

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.

Blood and Serum Assessments

- All blood samples will be obtained by venipuncture before investigational product administration. The average volume of blood drawn per visit will be approximately 5.0 mL.
- Refer to Section 12.2

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 2-1).

9.2.3.1 Adverse Events

9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

9.2.3.1.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) and is described in Section 12.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from screening through week 96 or EOS:

- the EOS visit (week 96) for a completed subject, or
- for subjects receiving investigational product (denosumab) and who withdraw full consent/assent prior to EOS, 30 days after the last dose of investigational product (denosumab), or
- for subjects receiving alternative osteoporosis medication/s or observation only and who withdraw consent/assent prior to EOS, until consent/assent is withdrawn, are reported using the Event CRF.

9.2.3.1.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the 20170534 informed consent/assent through the EOS visit or for subjects who withdraw full consent/assent prior to EOS 30 days after the last day of treatment with investigational product (denosumab) are reported using the Event CRF. Any serious adverse events that occur prior to signing the 20170534 informed consent/assent can be reported using the electronic Serious Adverse Contingency Report Form for 20130173 as per 20130173 protocol Section 9.2.1.2.

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.

There are no anticipated serious adverse events that are not planned to be reported individually in an expedited manner.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 12.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

Since the criteria the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life-threatening status), it will be left to the investigator's judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.

9.2.3.1.1.3 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. Per local requirements in some countries, 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 using the electronic Serious Adverse Event Contingency Report form.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product (denosumab).

The method of recording, evaluating, and assessing causality of adverse events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 12.4.

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.

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

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

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

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

otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Section 12.4.

All new information for previously reported serious adverse events including those that initiated during Study 20130173 must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

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

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and, if indicated, female partners of male subjects**,** will be collected after the start of investigational product (denosumab) and until 5 months after the last dose of investigational product (denosumab).

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in

Section 12.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 12.5.

9.2.3.2 Vital Signs

The following measurements should be performed: systolic and diastolic blood pressure (if clinically acceptable by the Investigator), heart rate, respiratory rate, and temperature. Subject should be in a supine position in a rested and calm state for at least 5 minutes before heart rate 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.

Where the screening visit coincides with the Study 20130173 EOS visit, vital signs should not be repeated. Vital signs should be assessed if the Study 20130173 EOS and screening visits do not occur on the same day.

9.2.3.3 Other Safety

Knee Radiograph Anteroposterior

This will be performed only in subjects with open growth plates who do not have bilateral hardware. Radiographs of the knee assessed in Study 20130173 should be obtained. The knee for assessment of metaphyseal index during the study should be the knee assessed in Study 20130173, unless prohibited by presence of hardware, in which case an anteroposterior 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.

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 assessments should be submitted to the central imaging vendor.

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 screening and at 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 "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).

Any Other Safety procedures captured at EOS visit of Study 20130173 may be used as the baseline visit data for this study if the visit is combined.

9.2.4 Clinical Laboratory Assessments

Refer to Section 12.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 2-1) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator

must determine 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.

All protocol-required laboratory assessments, as defined in Section 12.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 2-1).

9.2.4.1 Pregnancy Testing

A highly sensitive (urine) pregnancy test should be completed within 7 days prior to initiation (day 1) and subsequent dosing of investigational product (denosumab) for female subjects who are at Tanner stage 2 (or higher) or have had menarche. For these subjects, a negative pregnancy test must be confirmed prior to administration of denosumab at all scheduled visits. Refer to Schedule of Activities (Table 2-1). Pregnancy tests should be performed for subjects receiving alternative OI medications as per label instructions.

Additional on-treatment pregnancy testing (urine) may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Worksheet, see Figure 12-2). Refer to Section 12.5 for contraceptive requirements.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

9.2.5 Antibody Testing Procedures

Blood sample(s) are to be collected (from denosumab treated subjects only) as specified in the Schedule of Activities (Table 2-1) for the measurement of antidenosumab binding antibodies. Antibody testing should be conducted for the Study 20130173 EOS visit and data will be transferred to the Study 20170534 screening visit. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further

characterized. Additional blood samples may be obtained to rule out antidenosumab antibodies during the study.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an antidenosumab antibody response may also be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months from the final scheduled antibody time point and continue until: (1) antibodies are no longer detectable; or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of denosumab. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing or testing for a longer period of time may be requested in the event of safety-related concerns.

9.2.6 Other Assessments

9.2.6.1 End of Study Visit

Per the 30 September 2021 DIL, all investigators were notified to immediately stop denosumab treatment and continue the study as per the normal schedule of assessments (without denosumab treatment). All subjects participating in the study will be followed for 24 weeks after their last dose of denosumab. At 24 weeks the End of Study (EOS) Assessments should be completed per the current Schedule of Activities (Table 2-1).

Subjects who were on denosumab (3 months or every 6 months treatment) and stopped denosumab more than 24 weeks ago should be scheduled for their EOS Visit at the next scheduled visit and have their EOS Visit assessments conducted per the current Schedule of Activities (Table 2-1).

Subjects on alternative or observational therapy that never taken denosumab should complete the EOS assessment at the next schedule visit s(Table 2-1)

If possible, the procedures of the week 96 EOS visit should be completed at the time of withdrawal with the following exception:

- Procedures involving X-ray radiation other than DXA assessment may not be performed if less than 3 months have elapsed since the previous radiographic assessment.
- DXA scans will only be performed if more than 30 days have elapsed since the previous assessment.

10. Statistical Considerations

10.1 Sample Size Determination

The number of subjects in this study will be determined by the number of subjects completing Study 20130173, and who are willing and able to participate in the long-term follow-up study. All statistical analyses will only involve descriptive statistics, and no formal hypothesis testing will be done. Therefore, no sample size calculation is necessary for this study.

For sample sizes ranging from 100 to 150 subjects, the 95% CI based on exact method for the incidence rate of a particular adverse event is calculated below (Table 10-1). If none of the subjects report a particular adverse event, then a true incidence rate of more than 3.6% for 100 subjects and 2.4% for 150 subjects is unlikely for that particular adverse event.

Table 10-1. Estimated 95% CI for Example Adverse Events of Interest Incidence Rate

Number of Subjects Reporting Adverse Event	Adverse Event Incidence Rate	
	Estimate (%)	95% CI (%)
0/100	0	(0.0, 3.6)
1/100	1	(0.0, 5.4)
5/100	5	(1.6, 11.3)
10/100	10	(4.9, 17.6)
0/120	0	(0.0, 3.0)
1/120	0.8	(0.0, 4.6)
6/120	5	(1.9, 10.6)
12/120	10	(5.3, 16.8)
0/150	0	(0.0, 2.4)
1/150	0.7	(0.0, 3.7)
8/150	5.3	(2.3, 10.2)
15/150	10	(5.7, 16.0)

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

Full Analysis Set

The full analysis set (FAS) includes all enrolled subjects who have provided informed consent/assent and have a non-missing enrollment date.

Safety Analysis Set

The safety analysis set includes all subjects in the FAS who received ≥ 1 dose of denosumab during Study 20130173.

DXA Analysis Set

The DXA analysis set includes all subjects in the FAS with baseline and ≥ 1 postbaseline valid DXA assessments for the endpoint of interest (lumbar spine, total hip or femoral neck) as provided by the central imaging vendor. Note that this subset could potentially be different from endpoint to endpoint due to missing data.

[redacted]

Metaphyseal Analysis Set

This analysis set includes all subjects in the 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 postbaseline.

Details on analysis sets will be included in the Statistical Analysis Plan.

10.2.2 Covariates

Not applicable for this study.

10.2.3 Subgroups

Not applicable for this study.

10.2.4 Handling of Missing and Incomplete Data

In general, analyses will be based on available data. Missing outcomes of interest will not be imputed. Missing dates will be imputed, the details of which will be included in the Statistical Analysis Plan.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the EOS, as defined in Section 5.3.1.

10.3.1 Planned Analyses

10.3.1.1 Interim Analysis and Early Stopping Guidelines

Not applicable for this study.

10.3.1.2 Primary Analysis

Primary analysis will occur upon completion of the study when **the last** subject completes the 24-week follow-up visit following the last dose of denosumab.

10.3.1.3 Final Analysis

No final analysis is planned as the primary analysis will occur at the end of the study.

10.3.2 Methods of Analyses

10.3.2.1 General Considerations

Statistical analysis in this study will be descriptive in nature and statistical inferences will be for guidance only. Descriptive statistics will be provided for baseline demographics and subject characteristics based on the FAS, and for all endpoints based on their respective analysis sets and within each pattern of treatment received during the study if data warrant. Continuous outcomes will be summarized by the number of non-missing values, mean, SD, median, lower and upper quartiles and minimum and maximum values. Nominal and ordinal categorical variables will be summarized using counts and percentages. All outcomes will be summarized for both the FAS and within each pattern of treatment received during the study**, if warranted by the data**. Detailed definition of treatment patterns will be provided in the Statistical Analysis Plan.

Details will be described in the Statistical Analysis Plan.

10.3.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The analysis of primary endpoints will be descriptive, and details will be provided in the SAP.
Secondary	The analysis of secondary endpoints will be descriptive, and details will be provided in the SAP.

Exploratory	For each exploratory endpoint, descriptive statistics will be provided per described in Section 10.3.2.1 and details will be provided in the SAP.

SAP = statistical analysis plan

10.3.2.3 Safety Analyses

10.3.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be provided as described in Section 10.3.2.1 for both the FAS and within each pattern of treatment received during the study if data warrant for rate of adverse events, serious adverse events, and adverse events of special interest.

10.3.2.3.2 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product (denosumab), and adverse events of special interest will also be provided. The adverse events of special interest will include changes in growth plate morphology, severe or symptomatic hypocalcemia, ONJ, abnormal molar eruption, hypercalcemia, and abnormal mandibular shaping.

10.3.2.3.3 Laboratory Test Results

Actual values and changes from baseline in each parameter will be descriptively summarized at each visit. For serum calcium, phosphorus, and alkaline phosphatase (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 done for both the FAS and within each pattern of treatment received during the study if data warrant. Subjects with missing data for a scheduled visit will not contribute to the tabulation for that time point (no imputation).

10.3.2.3.4 Vital Signs

Descriptive statistics of the actual values and changes from baseline in vital signs (heart rate, respiration rate, temperature) will be presented by visit for both the FAS and within each pattern of treatment received during the study if data warrant.

Subjects with missing data for a scheduled visit will not contribute to the tabulation for that time point (no imputation).

10.3.2.3.5 Antibody Formation

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 subjects treated with denosumab in this study.

10.3.2.3.6 Exposure to Investigational Product

Subjects are considered exposed to denosumab if they received at least 1 dose of denosumab during the study.

Administration dates and doses of denosumab will be collected and cumulative denosumab exposure will be recorded and summarized using descriptive statistics.

10.3.2.3.7 Exposure to Non-Amgen Product: Alternative Osteoporosis Medication/s

Subjects are considered exposed to alternative osteoporosis medication/s if they received at least 1 dose of alternative osteoporosis medication/s during the study.

Administration dates, routes, and doses of alternative osteoporosis medication/s will be collected and cumulative alternative osteoporosis medication/s will be recorded and summarized using descriptive statistics.

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12. Appendices

12.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ADT	androgen deprivation therapy
AFF	atypical femoral fractures
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BIL	bilirubin
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
[redacted]	
CFR	U.S. Code of Federal Regulations
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DIL	Dear Investigator Letter
DILI	drug-induced liver injury
DXA	dual X-ray absorptiometry
Early Termination	defined as the date when a subject decides to end study early
EDC	electronic data capture
End of Study	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOS	End of Study
FAS	full analysis set
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GiOP	glucocorticoid-induced osteoporosis
HCP	healthcare provider
ICF	informed consent form
ICH	International Council for Harmonisation

Abbreviation or Term	Definition/Explanation
ID	identification
IEC	Independent Ethics Committee
Ig	immunoglobulin
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
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
Kd	dissociation equilibrium constant
NCT	National Clinical Trials
OI	osteogenesis imperfecta
ONJ	osteonecrosis of the jaw
PIP	Pediatric Investigational Plan
PK	pharmacokinetics
RANK	receptor activator of nuclear factor kappa-B
RANKL	receptor activator of nuclear factor kappa-B ligand
Q3M	every 3 months
Q6M	every 6 months
SAP	Statistical Analysis Plan
SC	subcutaneous
[redacted]	
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study day 1	defined as the day of the first dose of investigational product (denosumab) on the 3-Month dosing schedule for subjects: –that transition from 20130173 EOS to investigational product 3-Month Dosing Regimen –or currently enrolled on any arm of the 20170534 PA1 that consent/assent to investigational product 3-Month dosing schedule for the first time

Abbreviation or Term	Definition/Explanation
TBL	total bilirubin
TOIFF	typical OI femur fractures
ULN	upper limit of normal

12.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the central laboratory and/or by Amgen. Highly sensitive urine pregnancy test will be performed locally. 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). Under exceptional circumstances (eg, pandemic), scheduled study clinical laboratory tests may be performed by the investigative site; this should be agreed with the study team in advance. Data will be entered into Rave by the site. Blood collection may be performed by a qualified individual at the subject's home, in lieu of a site visit, on days 10 and 30 following visits at week 12 and week 24.

The central laboratory will be responsible for all serum chemistry, hematology as well as serology assessments. The central laboratory will also conduct assessments of vitamin D, [redacted] The central laboratory (PPD) will perform the antidenosumab antibody assay. Amgen will be responsible for performing the neutralizing antidenosumab antibody assay on binding positive samples (if necessary). The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all serum samples.

All samples will be non-fasting and obtained by venipuncture before investigational product (denosumab) or alternative osteoporosis medication administration, when applicable. The date and time of blood collection will be recorded in the subject's medical record.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12-1. Analyte Listing

Central Laboratory: Chemistry	Central Laboratory: Hematology	Other Labs
Sodium	RBC	Central Laboratory:
Potassium	Hemoglobin	25 (OH) vitamin D
Chloride	Platelets	[redacted]
Bicarbonate	WBC	
Total protein	Differential	Ur ne calcium
Albumin-corrected calcium	• Neutrophils	
Calcium	• Eosinophils	Local Laboratory
Magnesium	• Basophils	Urine pregnancy
Phosphorus	• Lymphocytes	
Glucose	• Monocytes	Central Laboratory (PPD)

Central Laboratory: Chemistry	Central Laboratory: Hematology	Other Labs
BUN Creatinine Total bilirubin ALP AST (SGOT) ALT (SGPT) GFR		Antidenosumab antibody assay <u>Amgen</u> Antidenosumab neutralizing antibody assay (if necessary)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; [redacted]; BUN = blood urea nitrogen; GFR = glomerular filtration rate; RBC = red blood cell count; [redacted]; SGOT = serum glutamic-oxaloacetic transaminase; SGPT - serum glutamic-pyruvic transaminase; WBC = white blood cell count

12.3 Appendix 3. Study Governance Considerations

Independent Adjudication Committee(s)

Potential events of ONJ will be adjudicated by an independent adjudication committee.

Typical osteogenesis imperfecta femur fractures will be read by central imaging vendor providing standard description of all fractures.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent/assent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)] by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent/assent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product (denosumab).

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent/assent document that Amgen distributes to the site. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

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 U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

Subjects completing Study 20130173 and are willing to enroll in this study will be included.

Informed Consent/Assent Process

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.

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

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product (denosumab) is administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (defined as an individual or other body authorized under applicable law to consent/assent, on behalf of a prospective subject, to the subject's participation in the clinical study) will then be required to sign a statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent/assent was obtained before the subject was enrolled in the study and the date the written

consent/assent was obtained. The authorized person obtaining the informed consent/assent must also sign the informed consent/assent form.

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 unless it is a local requirement. The investigator shall then inform the primary care physician. 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/assent 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 informed consent/assent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent/assent discussion. Subject withdrawal of consent/assent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

Subjects must be reconsented/assented to the most current version of the informed consent/assent form(s) during their participation in the 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 participants consent must be taken. Per 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 original signed informed consent/assent form is to be retained in accordance with institutional policy, and a copy of the informed consent/assent form(s) must be provided to the subject or the subject's legally authorized representative.

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

informed consent/assent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9).

The informed consent form (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.

Data Protection/Subject Confidentiality

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

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 Case Report Form (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 informed consent/assent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental 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/assent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to 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 need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must 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 must qualify for authorship, and all those who qualify are to be listed. Each author must 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.

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

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

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

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of

study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

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

Case report forms (CRF) must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

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

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) system (if used, such as subject identification [ID] and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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 CRFs, informed consent/assent forms, and subject identification list
- Study files containing the protocol with all amendments, 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, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

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

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product (denosumab) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product (denosumab) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

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.

12.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event, and Serious Adverse Event Recording
• When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant adverse event /serious adverse event information in the Event case report form (CRF).

- The investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to denosumab; and
  - Action taken.
- If the severity of an adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Events CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contact research organization (CRO) in lieu of completion of the Events CRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen Global Patient Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

The Common Terminology Criteria for Adverse Events, version 4.03 which is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product (denosumab) and other antiresorptive therapy and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product (denosumab) and the event.
- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen Global Patient Safety to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
- For all deaths, available autopsy reports and relevant medical reports should be provided to Amgen Global Patient Safety]
- New or updated information will be recorded in the originally completed Events CRF.
- The investigator will submit any updated serious adverse event data to Amgen Global Patient Safety within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool

- The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system.
- If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Event Contingency Report Form (see Figure 12-1) within 24 hours of the investigator's knowledge of the event.

- The site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on the 20170534 eSAE Contingency Report Form (see Figure 12-1).
  • Once the study has ended, serious adverse event(s) will be reported to Amgen (regardless of causality) if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Report Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions
The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

FORM-056006 *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

AMGEN **Study #** 20170534 **denosumab (Prolia)**	**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 eeath. 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 theEvent may have been caused by IP or an Amgen device used to administer the IP? Denosumab No✓ Yes✓	**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria:	01 Fatal	03 Required/prolonged hospitalization	05 Congenital anomaly / birth defect
	02 Immediately life-threatening	04 Persistent or significant disability /incapacity	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:		**Date of Initial Dose** Day Month Year	**Prior to, or at time of Event** **Date of Dose** Day Month Year	**Dose**	**Route**	**Frequency**	**Action Taken with Product** 01 Still being Administered 02 Permanently discontinued 03 Withheld	**Lot # and Serial #**
denosumab	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN **Study #** 20170534 **denosumab (Prolia)**	**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 #** 20170534 **denosumab (Prolia)**	**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.		

12.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for female of childbearing potential OR who have reached puberty are outlined in Section 6.2.

Female subjects of childbearing potential who have reached puberty must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for 5 months after the last dose of denosumab. Subjects receiving alternative osteoporosis medication/s of the investigator's choice should be counseled per specific drug requirements. Subjects not receiving any treatment (observation only) are not required to use contraception.

Definition of Females of Childbearing Potential

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

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Tanner grade < 2

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

Note: Failure rate of < 1% per year when used consistently and correctly.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion

- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, postovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 5 months after the last dose of denosumab.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 5 months after the last dose of denosumab. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- 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.

- Any serious adverse event occurring as a result of a poststudy pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 12.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 8.1 for details).

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 5 months after the last dose of denosumab.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 203.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 5 months after the last dose of denosumab after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20170534

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 age (at onset):** ____ (in years)

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 last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Amgen Proprietary - Confidential

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20170534

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 age (at onset):** ____ (in years)

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:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

12.6 Appendix 6. Sample Storage and Destruction

Any blood sample collected according to the Schedule of Activities (Table 2-1) 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/assent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the osteogenesis imperfecta, the dose response and/or prediction of response to denosumab, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent/assent.

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 12.3 for subject confidentiality.

12.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [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 investigational product (denosumab) or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

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

Denosumab and other protocol-required therapies (including other antiresorptive therapies), as appropriate, should be discontinued permanently and the subject should be followed according to the recommendations in Section 12.3 (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2 x upper limit of normal (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 BIL glucuronidation (eg, indinavir, atazanavir)

– Alpha-one antitrypsin deficiency

– Alcoholic hepatitis

- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis (e)
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

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

The following rules are recommended for withholding of denosumab and other protocol-required therapies (including antiresorptives):

- 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, antiresorptive therapies, and other protocol-required therapies, as appropriate, should be withheld pending investigation into alternative causes of DILI. If investigational product(s) is withheld, the subject is to be followed according to recommendations in Section 12.3 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 (See: Criteria for Rechallenge of Amgen Investigational Product, Other Antiresorptive Therapies, and Other Protocol-required Therapies After Potential Hepatotoxicity).

Criteria for Rechallenge of Amgen Investigational Product, Other Antiresorptive Therapies, 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, other antiresorptive therapies, and other protocol-required therapies, as appropriate should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in "Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product, Other Antiresorptive Therapies, and Other Protocol-required Therapies Due to Potential Hepatotoxicity") should never be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, 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 Case Report Form (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to 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 12.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product (denosumab) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI or who experience AST or ALT elevations $>$ 3 x ULN or 2-fold increases above baseline values for subjects with elevated values before drug 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, ALPBIL (total and direct), and INR within 24 hours
- In cases of TBL $>$ 2 x ULN or INR $>$ 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product (denosumab) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL.

The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig)G, antinuclear antibody antismooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of investigational product (denosumab) and protocol-required therapies.

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

Amendment 5

Protocol Title: Multicenter, Single-arm Open-label Extension Study to Assess Long-term Safety and Efficacy of Current or Prior Treatment With Denosumab in Children/Young Adults With Osteogenesis Imperfecta

Amgen Protocol Number 20170534

Amendment Date: 02 February 2022

Rationale:

The intent of study 20170534 was a safety extension after treatment with denosumab for 36 months on a 6-month dosing regimen and where there was no protocol mandated treatment. This would allow for the collection of longer-term safety data on denosumab as well as an assessment of the impact of stopping denosumab and switching to an alternative treatment on efficacy.

In protocol amendment 3, a 3-month dosing regimen was introduced given the less than expected increase in bone mineral density (BMD) on 6-month dosing and pharmacokinetics/pharmacodynamics (PK/PD) data showing low denosumab levels at 3 months. Starting from 30 September 2021, due to the life-threatening events of hypercalcemia reported on denosumab use in the pediatric osteogenesis imperfecta (OI) study, further dosing on 20170534 was stopped, and subjects were to be followed for safety for 24 weeks following the last dose of denosumab. This urgent safety measure resulted in early trial termination for severe and serious hypercalcemia on a 3-month dosing regimen.

Given the limited amount of available data for efficacy analysis, the analysis of the secondary endpoints is changed in this protocol amendment to ensure that only quality data is presented as an endpoint. The secondary efficacy endpoints of fracture and growth velocity are removed, and BMD Z-score is clarified given the multiple treatment sequences in the trial. Adverse events of fracture, including femur fractures, will be presented in the adverse event tables.

The primary objective and endpoint in this study is safety and is unchanged.

Amendments to the protocol include:

- Deletion of secondary efficacy endpoints of fracture and growth velocity
- Clarification of the secondary endpoint of bone mineral density (BMD) Z-score assessed at 6, 12, and 24 months
- Deletion of the exploratory endpoint for BMD and bone mineral content
- Clarif cation of the exploratory endpoint of [redacted]
- Deletion of investigational product administration from additional 12-week safety follow-up column in the Schedule of Activities
- Deletion of the growth velocity and vertebral fracture analysis sets as a result of the deletion of the corresponding endpoints
- Deletion of subgroups analysis information from the protocol
- Administrative and typographical updates for consistency and clarity

Amendment 4

Protocol Title: Multicenter, Single-arm Open-label Extension Study to Assess Long term Safety and Efficacy of Current or Prior Treatment With Denosumab in Children/Young Adults With Osteogenesis Imperfecta

Amgen Protocol Number 20170534

NCT Number NCT03638128

Amendment Date: 09 November 2021

Rationale:

This protocol is being amended to:

- Address Risk Level 1 safety concern of hypercalcemia. The protocol has been updated to stop all dosing of denosumab due to Data Monitoring Committee (DMC) decision.
- Implement a safety follow-up period for 24 months following the last dose of denosumab
- Stop enrollment to the study
- Update risks and benefits to reflect that the benefit of denosumab does not outweigh the risks
- Update safety language per newest protocol template
- Administrative and editorial updates

Amendment 3

Protocol Title: Multicenter, Single-arm Open-label Extension Study to Assess Long-term Safety and Efficacy of Current or Prior Treatment With Denosumab in Children/Young Adults With Osteogenesis Imperfecta

Amgen Protocol Number Denosumab 20170534

Superseding Amendment Date: 14 January 2021

Superseding Amendment 3 Summary of Changes:

Rationale:

Additional updates were made to harmonize content with protocol 20130173 and remove a reference to the Safety Report Form since reporting will now be collected on the Events electronic case report form, and the Safety Report Form will be retired.

Changes include, but are not limited to:

- Updates to Schedule of Activities including:
  - Link chemistry activity to footnote letter u (At all study visits signs and symptoms of hypocalcemia will be assessed and subjects reminded of importance of taking calcium and vitamin D.)
  - Link chemistry activity on days 10 and 30 after weeks 12 and 24 to footnote letter v (On days 10 and 30, blood collection may be performed by a qualified individual at the subject's home, in lieu of a site visit.)
  - Remove separate serious adverse event assessment since this is included in the adverse event assessment
  - Replace assessment of clinical fracture recording continuously throughout study with an assessment at visit day 1, days 10 and 30 after day 1, and at every 12 week visit including the final visit
- Clarify that blood collection on days 10 and 30 after week 12 and 24 visit can be performed by a qualified individual at the subject's home
- Update timing of activities in the protocol to be consistent with the schedule of activities table
- Remove serum as a type of pregnancy test to be used
- Remove the reference to the Safety Report Form from Appendix 4

Amendment 3

Protocol Title: Multicenter, Single-arm Open-label Extension Study to Assess Long-term Safety and Efficacy of Current or Prior Treatment With Denosumab in Children/Young Adults With Osteogenesis Imperfecta

Amgen Protocol Number Denosumab 20170534

Amendment Date: 17 November 2020

Rationale:

The protocol is being amended to harmonize content with protocol 20130173 and to address Food and Drug Administration (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.

-Add the assessment of signs and symptoms of hypocalcemia to be assessed 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.

-Administration, typographical and formatting changes were made throughout the protocol. Updates have been implemented to align with the current template.

Superseding Amendment 2

Protocol Title: Multicenter, Single-arm Open-label Extension Study to Assess Long term Safety and Efficacy of Current or Prior Treatment With Denosumab in Children/Young Adults With Osteogenesis Imperfecta

Amgen Protocol Number (Denosumab) 20170534

EudraCT number 2018-000550-21

NCT number NCT03638128

Amendment 2 Date:	31 March 2020
Superseding Amendment 2 Date	30 April 2020

Superseding Amendment 2 Rationale:

The superseding amendment 2 is being issued to:

- Clarify that Day 10 and Day 30 assessments are only required for subjects who started on 3-month dosing regimen for the first time.
- Update Schedule of Activities for chemistry, hematology, and DXA scan and some editorial changes in footnotes.

Amendment 2 Rationale:

This protocol is being amended to:

- Modify inclusion criteria 102 to indicate that
    - Subjects who do no reconsent to transition to 3-Month Dosing Regimen on 20130173 will also be offered participation in this study.
    - Subjects who Early terminated from Study 20130173 as a result of meeting BMD Z-score IP stopping criteria and was required to early terminate from the study in order to receive alternative OI medication through medical insurance.
- Schedule of Activities
    - Include schedule of activities at visits on day 10 and day 30.

  - Report the schedule of activities in every 12 weeks instead of every month
  - Remove the option of substance abuse for General and Safety Assessment
  - Updated Schedule of Activities time points; and footnotes with the timelines and definition of the procedures/tests conducted for the general and safety, laboratory, and study specific assessments and study treatments

- Clarify that 25 (OH) Vitamin levels should be collected at Screening.

Other Changes:

- Updated the secondary objectives and endpoints with inclusion of the 3-month dosing regimen to the Study 20130173 baseline.
- Updated the additional risks of hypercalcemia following denosumab discontinuation or at the end of the dosing interval when a subject is still receiving investigational product in patients with growing skeletons.
- Updated reported adverse events as of 27 May 2019.
- Updated the strategies to minimize hypercalcemia.
- Updated dosage adjustments, delays, rules for withholding or restarting permanent discontinuation of Amgen Investigational Product (denosumab)
- Updated the language for efficacy assessments to indicate the purpose/timeframe of the conducted assessments of radiographic, dual-energy absorptiometry, and spine radiographics.
- Updated the definition for End of Study
- Updated subject enrollment
- Updated other protocol-required therapies
- Updated analysis sets
- Updated statistical analysis methods for Primary/Secondary endpoints of Efficacy and Safety analysis
- Administrative and editorial updates

Amendment 2

Protocol Title: Multicenter, Single-arm Open-label Extension Study to Assess Long term Safety and Efficacy of Current or Prior Treatment With Denosumab in Children/Young Adults With Osteogenesis Imperfecta

Amgen Protocol Number (Denosumab) 20170534

EudraCT number 2018-000550-21

NCT number 03638128

Amendment Date: 31 March 2020

Rationale:

This protocol is being amended to:

- Modify inclusion criteria 102 to indicate that
    - Subjects who do no reconsent to transition to 3-Month Dosing Regimen on 20130173 will also be offered participation in this study.
    - Subjects who Early terminated from Study 20130173 as a result of meeting BMD Z-score IP stopping criteria and was required to early terminate from the study in order to receive alternative OI medication through medical insurance.
- Schedule of Activities
    - Include schedule of activities at visits on day 10 and day 30.
    - Report the schedule of activities in every 12 weeks instead of every month
    - Remove the option of substance abuse for General and Safety Assessment
    - Updated Schedule of Activities time points; and footnotes with the timelines and definition of the procedures/tests conducted for the general and safety, laboratory, and study specific assessments and study treatments
- Clarify that 25 (OH) Vitamin levels should be collected at Screening.

Include that the Pharmacokinetic/Pharmacodynamics analysis will be conducted on all subjects on 3-month dosing regimen to further characterize dosing in the pediatric population with

osteogenesis imperfecta to add to the data obtained during the trial during the 6-month dosing regimen trial.

Other Changes:

- Updated the secondary objectives and endpoints with inclusion of the 3-month dosing regimen to the Study 20130173 baseline.
- Updated the additional risks of hypercalcemia following denosumab discontinuation or at the end of the dosing interval when a subject is still receiving investigational product in patients with growing skeletons.
- Updated reported adverse events as of 27 May 2019.
- Updated the strategies to minimize hypercalcemia.
- Updated dosage adjustments, delays, rules for withholding or restarting permanent discontinuation of Amgen Investigational Product (denosumab)
- Updated the language for efficacy assessments to indicate the purpose/timeframe of the conducted assessments of radiographic, dual-energy absorptiometry, and spine radiographics.
- Updated the definition for End of Study
- Updated subject enrollment
- Updated other protocol-required therapies
- Updated analysis sets
- Updated statistical analysis methods for Primary/Secondary endpoints of Efficacy and Safety analysis
- Administrative and editorial updates

Amendment 1

Protocol Title: Multicenter, Single-arm Open-label Extension Study to Assess Long term Safety and Efficacy of Current or Prior Treatment with Denosumab in Children/Young Adults with Osteogenesis Imperfecta

Amgen Protocol Number Prolia 20170534

NCT Number: 03638128

EudraCT Number: 2018-000550-21

Amendment Date: 11 July 2019

Rationale:

The protocol is being amended to:

- Clarify that investigational product in this study protocol refers to denosumab, and that there is no protocol-required investigational product in this trial
- Include subject incidence of adverse events of special interest in safety monitoring of the primary endpoint
- Clarify that the change in growth velocity for the secondary endpoint is from baseline and from Study 20130173 baseline
- Remove language for screening and screen failures
- Clarify that subjects may receive denosumab, alternative osteoporosis medication/s of investigator's choice administered per local standard of care; or observation only (no intervention)
- Clarify in the procedures of the synopsis that those greater than Tanner 1 will need pregnancy testing
- Clarify language for medical history, completion of screening assessment on Day 1 of study, and Screening and Study Day 1 visit coinciding with Study 20130173 to Study 20170534 in the footnotes of the schedule of activities
- Add in the schedule of activities that X-rays should be sent to the central imaging vendor for all non-vertebral fractures occurring after enrollment, and that calcium and vitamin D are required for patients receiving denosumab
- Clarify language for alternative osteoporosis medication/s product background
- Update language/definition for atypical femoral fracture events (AFF) and remove AFF adjudication from study protocol. Fractures will be reviewed as typical osteogenesis imperfecta femur fractures.
- Update language for eligibility in the study population
- Clarify exclusion criteria for prior/concomitant therapy and other exclusions
- Clarify language for enrollment study period and screen failures

- Update language for treatments (ie, defining study treatment)
- Added footnote for androgens in the list of proscribed therapy
- Revise text for treatment assignment to treatment administration
- Clarify dosing adjustments and discontinuation of denosumab and/or alternative medication
- Update reasons for stopping administration of denosumab to include if a decline in lumbar spine bone mineral density (BMD) Z-score by 0.5 units or changes in growth plate morphology are observed in 12 rather than 6-month monitoring, or if severe hypersensitivity is observed
- Add language for alternative osteoporosis medication/s; changes or cessation will be at investigator discretion consistent with local standard of care
- Update language for discontinuation criteria (to include reasons for withdrawl), discontinuation of study treatment, and discontinuation from study treatment
- Clarify text for screening and enrollment
- Update language for treatment period and safety follow-up/end of study
- Clarify occurrence of physical examinations, physical measurements, and antibody testing as well as efficacy, safety, and clinical assessments per Screening visit and Study 20130173 month 36 visit
- Update language for adverse events and serious adverse events
- Add that vital signs should include measurement of systolic and diastolic blood pressure
- Update language for safety assessment of the knee radiograph anteroposterior
- Update text for pregnancy testing to include that additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulation
- Clarify language for end of study visit
- Update reference list to include new citations
- Update definition of Study Day 1 in the abbreviations list
- Remove retired language related to self-evident corrections (SEC)
- Remove retired pregnancy and lactation notification forms and replace with updated forms
- Make editorial, typographical, and formatting changes throughout the document