Title: An Open-label, Ascending Multiple-dose Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Romosozumab in Children and Adolescents With Osteogenesis Imperfecta

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Date: Original: 09 February 2018
Amendment 1: 27 April 2020
Amendment 2: 26 May 2020
Amendment 3: 19 February 2021
Superseding Amendment 3: 28 February 2023

Investigator's Agreement

I have read the attached protocol entitled "An Open-label, Ascending Multiple-dose Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Romosozumab in Children and Adolescents with Osteogenesis Imperfecta" dated **28 February 2023** and agree to abide by all provisions set forth therein. I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

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

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

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

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

_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: An Open-label, Ascending Multiple-dose Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Romosozumab in Children and Adolescents with Osteogenesis Imperfecta

Study Phase: 1b

Indication: Osteogenesis Imperfecta (OI)

Primary Objective:

- To evaluate the pharmacokinetics (PK) profile following multiple subcutaneous (SC) doses of romosozumab in children and adolescents with OI

Secondary Objective:

- To evaluate the safety, tolerability, and immunogenicity profile following multiple SC doses of romosozumab in children and adolescents with OI
- To evaluate the pharmacodynamic (PD) profile following multiple SC doses of romosozumab in children and adolescents with OI

Hypothesis:

Romosozumab PK and PD, including the effects on bone mineral density (BMD) and bone turnover markers (procollagen type I N-terminal propeptide [P1NP] and serum type I collagen C-telopeptide [CTX]), will aid in the selection of the dose for the subsequent efficacy and safety study in pediatric subjects with OI. Romosozumab will be safe and well tolerated following multiple SC dose administrations in children and adolescents with OI.

Primary Endpoint:

- Romosozumab serum PK parameters: maximum-observed concentration (C_{max}), time to C_{max} (t_{max}), area under the curve (AUC) and terminal half-life ($t_{1/2}$)

Secondary Endpoints:

- Treatment-emergent adverse events, including events of injection site reactions and changes in cranial nerve function, vital signs, electrocardiograms, physical examinations, and safety laboratory tests, including serum calcium
- Incidence of anti-romosozumab antibodies
- Bone turnover markers including serum P1NP and serum type I collagen C-telopeptide (sCTX) measurements.
- Lumbar spine BMD, bone mineral content (BMC), bone area, and BMD Z-score as assessed by dual-energy X-ray absorptiometry (DXA)

Study Design:

This is a multicenter, open-label, ascending multiple-dose study to evaluate romosozumab in ambulatory children (5 to less than 12 years of age) and adolescents (12 to less than 18 years of age) with OI.

At least 16 subjects will be enrolled into sequential cohorts 1 to 4 (4 per cohort). All subjects will receive a total of [redacted] SC doses of romosozumab administered every [redacted] Subjects in cohorts 1 (12 to less than 18 years of age) and 2 (5 to less than 12 years of age) will be administered romosozumab [redacted] mg/kg SC [redacted] Subjects in cohorts 3 (12 to less than 18 years of age) and 4 (5 to less than 12 years of age) will receive romosozumab [redacted] mg/kg SC [redacted] If the exposure and PD effects are insufficient at [redacted] and [redacted] mg/kg, at least 4 subjects each will enroll into cohorts 5 (12 to less than 18 years of age) and 6 (5 to less than 12 years of age) and will receive romosozumab [redacted] mg/kg SC [redacted] All subjects will receive daily supplementation with calcium and vitamin D.

The planned dose levels and cohorts are described in the below table.

Planned Dose Levels

Cohort #	Age Group (years of age)	Dose[a]	Dosing Day	N (active)
1	12 to less than 18	[redacted]		4
2	5 to less than 12			4
3	12 to less than 18			4
4	5 to less than 12			4
5 (optional)	12 to less than 18			4
6 (optional)	5 to less than 12			4

[a] All doses will be administered subcutaneously

As a precautionary measure consistent with pediatric research, dose cohorts, starting with the lowest dose level, will be recruited so that adolescents 12 to less than 18 years of age will be enrolled first (n = 4) at each dose level, before children 5 to less than 12 years of age (n = 4) for the same dose level.

A dose level review meeting (DLRM) will be held to review safety data for the purposes of making recommendations before escalation to the next higher dose or expansion to a younger age cohort. The dose level review team (DLRT) will be composed of, at a minimum, the investigators actively enrolling subjects at the time of the meeting (ie, have subjects in screening or already enrolled), the Amgen Medical Monitor, and Amgen Global Safety Officer or designated safety scientist, Amgen Clinical Research Study Manager or designee, and biostatistics representative or designee. Additional members may be added as needed (eg, PK scientist). The DLRT voting members include the principal investigator or designee, Amgen Medical Monitor and Amgen Global Safety Officer or designee. The DLRT voting members are responsible for making dosing recommendations, which may include escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), de-escalation to a lower dose; continuation, delay, or termination of dosing; or repetition or expansion of a cohort. Clear stopping rules will be followed, and ad hoc DLRMs will be held if necessary. All available study data, including demographics, medical history, concomitant medications, adverse events, electrocardiograms, vital signs, and clinical laboratory test results will be reviewed. The medical monitor will review data on an ongoing basis throughout the duration of the study.

Investigators who are not actively enrolling subjects at the time of the DLRM will not participate in the DLRM. They will be informed of the DLRT recommendations.
DLRMs will take place at the following time points (Refer to Study Design and Treatment Schema):

- DLRM 1
  - After 2 subjects in cohort 1 complete 6 weeks on study
  - DLRM 1 will enable enrollment into cohorts 2 and 3
- DLRM 2a
  - May be conducted if escalation to the [redacted] mg/kg dose level is deemed necessary based on available PK and PD data from cohorts 1 and 3
  - If necessary, DLRM 2a will be conducted after 2 subjects in cohort 3 complete 6 weeks on study
  - DLRM 2a will enable enrollment into cohort 5
- DLRM 2b
  - After 2 subjects in both cohorts 2 and 3 complete 6 weeks on study
  - DLRM 2b will enable enrollment into cohort 4

- DLRM 3
  - May be conducted if escalation to the [redacted] mg/kg dose level is deemed necessary based on available PK and PD data from cohorts 1 through 4
  - If necessary, DLRM 3 will be conducted after 2 subjects in both cohorts 4 and 5 complete 6 weeks on study
  - DLRM 3 will enable enrollment in cohort 6

Sample Size:

The sample size is based on practical considerations. At least 16 subjects (or 24 depending on emerging results) will be enrolled into the study.

Summary of Subject Eligibility Criteria:

Ambulatory male and female children and adolescents 5 to less than 18 years of age with a clinical diagnosis of OI will be enrolled into the study.

For a full list of inclusion and exclusion criteria, please refer to Sections 4.1 and 4.2.

Investigational Product

Amgen Investigational Product Dosage and Administration:

Romosozumab for SC administration is manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Romosozumab is provided in a 3 cc sterile vial filled with a 1 mL deliverable volume of 90 mg/mL romosozumab.

Romosozumab will be administered as a SC injection on days [redacted] and [redacted] Refer to table above entitled **Planned Dose Levels** for further details on dose levels.

All SC injections must be administered by authorized site personnel. Refer to the Investigational Product Instruction Manual (IPIM) for instructions.

Other Protocol-required Therapies: All subjects will receive daily supplements of at least 30-50 mg/kg per day to a maximum of 1000 mg elemental calcium and at least 800 IU vitamin D to minimize the risk of hypocalcemia for the duration of the study.

Calcium and vitamin D supplements will not be provided by Amgen.

Study Procedures:

Screening

After written informed consent has been obtained, all screening procedures and tests that establish study eligibility will be performed within 35 days prior to the day 1 visit. Study procedures are summarized in the Schedule of Assessments.

Serious Adverse Events will be collected from the time the Informed Consent Form is signed.

Treatment

A subject will be considered enrolled into the study once the subject is deemed eligible by the investigator based on screening and day 1 pre-dose assessments (as defined in the inclusion/exclusion criteria).

Investigational product will be dosed on study days [redacted] and [redacted] after completion of all pre-dose procedures. Safety assessments, including blood samples for anti-romosozumab antibodies, PK and PD measurements and time points are defined in the Schedule of Assessments (Table 6).

Follow-up

The study includes a [redacted] treatment period followed by a [redacted] follow-up period that starts from day 64. Safety assessments, including blood samples for anti-romosozumab antibodies, PK and PD measurements and time points through the end of study are defined in the Schedule of Assessments (Table 6).

All adverse events, including serious adverse events, and use of concomitant medication(s) will be collected throughout the study.

Day 169 or End of Study (EOS)

Subject's participation in the study will be complete once end of study (EOS) procedures are performed per the Schedule of Assessments on day 169. This visit will complete subject's

participation in this study. If there is a significant clinical or laboratory abnormality, the subject will be followed until resolution of the abnormality or until it is considered clinically stable.

Neutralizing antibody positive subjects will be followed for blood collections approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least one year (± 4 weeks) post administration of investigational product.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7.2 and the Schedule of Assessments (Table 6).

Statistical Considerations:

Descriptive statistics will be provided for selected demographics, safety, PK, and PD endpoints. Descriptive statistics on continuous measurements will include means, medians, standard deviations, quartiles and ranges, while categorical data will be summarized using frequency counts and percentages. Data will be presented and summarized for each dose cohort and at each time point.

The subject incidence of all adverse events will be tabulated by body system organ class and preferred term for each dose cohort. Clinical laboratory, electrocardiogram, and vital sign data will be listed and summarized as appropriate. The incidence(s) and percentage of subjects who develop anti-romosozumab antibodies (binding and, if positive, neutralizing) at any time will be tabulated. Graphical summaries of the data over time may also be provided for the raw data and percent change from baseline. The change from baseline in BMD Z-score at lumbar spine will be checked against the meta-analysis result from historical controls (Letocha et al, 2005; Rauch et al, 2009; Ward et al, 2011).

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

Sponsor:

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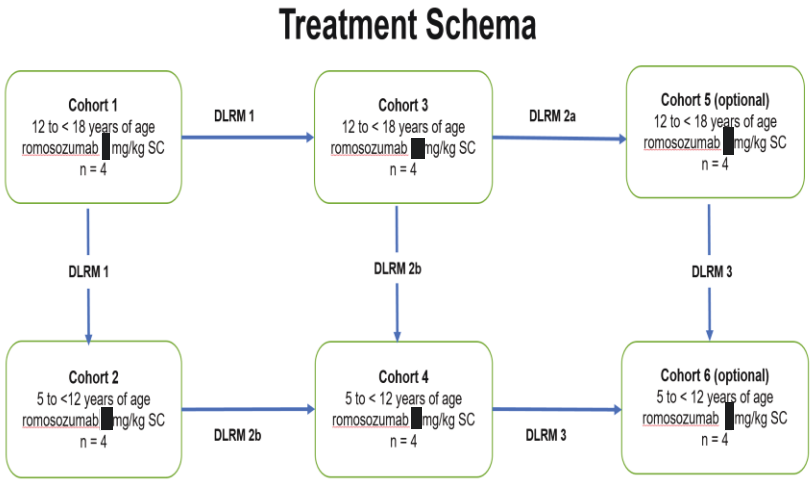
Study Design and Treatment Schema



DLRM 1 will be conducted after 2 subjects in cohort 1 complete 6 weeks on study. DLRM 1 will enable enrollment into cohorts 2 and 3. Enrollment into cohort 3 may begin after enrollment into cohort 1 is complete.

DLRM 2a may be conducted if escalation to the [redacted] mg/kg dose level is deemed necessary based on available PK and PD data from cohorts 1 and 3. If necessary, DLRM 2a will be conducted after 2 subjects in cohort 3 complete 6 weeks on study. DLRM 2a will enable enrollment into cohort 5. Enrollment into cohort 5 may begin after enrollment into cohort 3 is complete.

DLRM 2b will be conducted after 2 subjects in both cohorts 2 and 3 complete 6 weeks on study. DLRM 2b will enable enrollment into cohort 4. Enrollment into cohort 4 may begin after enrollment into cohort 2 is complete.

DLRM 3 may be conducted if escalation to the [redacted] mg/kg dose level is deemed necessary based on available PK and PD data from cohorts 1 through 4. If necessary, DLRM 3 will be conducted after 2 subjects in both cohorts 4 and 5 complete 6 weeks on study. DLRM 3 will enable enrollment into cohort 6. Enrollment into cohort 6 may begin after enrollment into cohort 4 is complete.

DLRM indicates dose level review meeting;
SC, subcutaneous.

Study Glossary

Abbreviation or Term	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AP	Anteroposterior
AST	aspartate aminotransferase
AUC	area under the curve
BMD	bone mineral density
BP	bisphosphonate
BTM	bone turnover markers
C_{max}	maximum-observed concentration
COL1A1	collagen type I alpha 1
COL1A2	collagen type I alpha 2
CRF	case report form
CTX	type I collagen c-telopeptide
DILI	drug-induced liver injury
DLRM	dose level review meeting
DLRT	dose level review team
DXA	dual-energy X-ray absorptiometry
ECHO	echocardiogram
eCRF	enrollment case report form
eSAE	electronic Serious Adverse Event
End of Study (EOS)	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Treatment	defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
EU	European Union
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgG2	Inmmunoglobulin 2
IP	investigational product
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board

Abbreviation or Term	Definition/Explanation
IU	international units
IVR system	Interactive Voice Response – telecommunication technology that is linked to a central computer in real time as an interface to collect and process information
IRT system	interactive response technology that is linked to a central computer in real time as an interface to collect and process information
Kg	kilogram
LLN	lower limit of normal
Mg	milligram
MRI	magnetic resonance imaging
OI	osteogenesis imperfecta
P1NP	procollagen type I N-terminal propeptide
PD	pharmacodynamic
PFS	prefilled syringe
PI	principal Investigator
PK	Pharmacokinetic(s)
PMO	postmenopausal osteoporosis
Primary Completion	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
QM	monthly
SC	subcutaneous
sCTX	Serum CTX
Source Data	Information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol specified investigational product(s)/protocol-required therapies is/are administered to the subject
T_{max}	time to C_{max}
ULN	upper limit of normal
US	United States

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1. OBJECTIVES

1.1 Primary

- To evaluate the pharmacokinetics (PK) profile following multiple subcutaneous (SC) doses of romosozumab in children and adolescents with osteogenesis imperfecta (OI)

1.2 Secondary

- To evaluate the safety, tolerability, and immunogenicity profile following multiple SC doses of romosozumab in children and adolescents with OI
- To evaluate the pharmacodynamic (PD) profile following multiple SC doses of romosozumab in children and adolescents with OI

2. BACKGROUND AND RATIONALE

2.1 Disease

Osteogenesis imperfecta is a group of genetic skeletal disorders characterized by increased bone fragility, low bone mass (Rauch and Glorieux, 2004), and increased bone turnover (Rauch et al, 2009) contributing to osteoporosis, fractures, and other conditions. OI is the most common form of primary osteoporosis in children with an estimated incidence of 1 per 25,000 live births (Byers, 2000; Mäkitie, 2013).

At least twelve types of OI have been identified based on clinical phenotype and underlying genetic defect (Marini and Blissett, 2013). The majority of individuals with OI are heterozygous for mutations in the type I collagen genes (collagen type I alpha 1 [COL1A1] or collagen type I alpha 2 [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 (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; Cheung and Glorieux, 2008). The most common OI presentation are listed below:

- Type I: the mildest form; no skeletal deformity; may have fractures with ambulation; vertebral scoliosis may also occur.
- Type II: the most severe form; multiple fractures and skeletal deformity in utero; usually fatal in the neonatal period.

- Type III: next-most-severe form after type II; severe skeletal deformities and bone fragility from a young age; fractures may occur from the in utero period through adulthood; scoliosis may be severe.
- Type IV: variable – mild to severe; moderate skeletal deformity.
- Type V: moderate skeletal deformity and moderate-to-severe bone fragility, with hypertrophic callus formation after some fractures, intraosseous membrane calcification, congenital dislocation of the radial head.

The medical management of pediatric OI includes the orthopedic prevention and treatment of fractures, bowing, and scoliosis. Clinicians have been using bisphosphonates in children with moderate to severe OI to reduce osteoclast activity and increase bone mineral density (BMD) (even though abnormal collagen is usually present [Byers, 2000]) with the aim of reducing fractures (Rauch and Glorieux, 2004; Ward et al, 2016). Clinical trials of bisphosphonate treatment in pediatric OI have consistently shown increases in BMD, with variable effects on fracture reduction, bone pain and quality of life (Castillo et al, 2009; Vuorimies et al, 2017). Teriparatide, a bone-forming agent, has been shown to increase bone mass and strength in adults with osteogenesis imperfecta, though its benefit in children is not known (Orwoll et al, 2014). Thus, an unmet need remains in children with OI.

2.2 Amgen Investigational Product Background

Sclerostin, the protein product of SOST, produced by the osteocyte, is an inhibitor of osteoblast-mediated bone formation (Balemans et al, 2001; Brunkow et al, 2001; Poole et al, 2005; Van Bezooijen et al, 2004; Winkler et al, 2003). Humans with inherited sclerostin deficiencies have high bone mass and BMD throughout the skeleton and are resistant to fractures (Hamersma et al, 2003; Vanhoenacker et al, 2003).

Administration of a sclerostin antibody, resulting in the blocking of the inhibitory effect of sclerostin on bone formation, has been shown to increase bone formation, BMD, and bone strength in multiple animal models (normal and osteoporotic rats, monkeys) (Li et al, 2009; Li et al, 2007a; Li et al, 2007b; Ominsky et al, 2010; Ominsky et al, 2011).

Romosozumab is a humanized monoclonal antibody immunoglobulin 2 (IgG2) that binds and inhibits sclerostin and has a dual effect on bone of increasing bone formation and decreasing bone resorption. Romosozumab stimulates new bone formation on trabecular and endocortical bone surfaces by stimulating osteoblastic activity resulting in increases in trabecular and cortical bone mass and improvements in bone structure and strength.

Romosozumab is indicated for the treatment of osteoporosis United States (US), or severe osteoporosis European Union (EU) in postmenopausal women at high risk for fracture (EVENITY® prescribing information).

Proof of biological activity for romosozumab was established in a first-in-human, ascending-single-dose study in healthy males and postmenopausal females, an ascending-multiple-dose study in healthy males and postmenopausal females with low bone mass and a phase 2 dose-ranging study in postmenopausal females with low bone mass. In all studies, treatment with romosozumab was generally well tolerated and resulted in a transient increase of the bone formation markers procollagen type I N-terminal propeptide (P1NP), osteocalcin (OC), and bone-specific alkaline phosphatase (BSAP), and a decrease in the bone resorption marker serum type I collagen C-telopeptide (sCTX) (McClung et al, 2014; Padhi et al, 2011; Padhi et al, 2014). Increases in BMD at the lumbar spine, total hip and femoral neck were also demonstrated by dual-energy X-ray absorptiometry (DXA) and Quantitative Computed Tomography (QCT) (Cosman et al, 2016; Graeff et al, 2015; Langdahl et al, 2017; McClung et al, 2014; Padhi et al, 2011; Padhi et al, 2014; Saag et al, 2017). With enduring gains in bone mass, the risk for patients to experience an osteoporotic fracture can be lessened, as demonstrated during the romosozumab phase 3 program as described below.

Study 20080289 compared romosozumab 210 mg QM with teriparatide 20 μg daily for 12 months in women with postmenopausal osteoporosis (PMO) at high risk for fracture and transitioning from bisphosphonate therapy. A statistically significant difference of 3.2% (95% CI 2.7 to 3.8; $p<0{\cdot}0001$) in favor of romosozumab in the percent change of total hip BMD (measured by DXA) through month 12 was observed (Langdahl et al, 2017).

In Study 20110174 of men with osteoporosis, subjects receiving romosozumab 210 mg QM had a statistically significant increase in BMD at the lumbar spine, femoral neck, and total hip at 6 and 12 months, compared with those receiving placebo. At month 12, subjects who received romosozumab demonstrated a mean percent increase in BMD at the lumbar spine from baseline of 12.1% (least squares mean) vs 1.2% for the placebo group. At the total hip and femoral neck, subjects who received romosozumab demonstrated a mean (least squares mean) percent increase in BMD from baseline of 2.5% vs - 0.5% for the placebo group, and 2.2% vs -0.2% for the placebo group, respectively.

In Study 20070337, women receiving romosozumab 210 mg SC QM had a statistically significant 73% reduction in the relative risk of a new vertebral fracture through 12 months compared with those receiving placebo (Cosman et al, 2016). Through month 24, romosozumab followed by denosumab reduced the relative risk of new vertebral fracture by a statistically significant 75% compared with placebo followed by denosumab. At month 36, treatment with romosozumab followed by denosumab resulted in continued significant increases in BMD at the lumbar spine, total hip, and femoral neck compared with placebo followed by denosumab (nominal $p < 0.001$ at each site).

In Study 20110142 in women with PMO at high risk for fracture, treatment with romosozumab 210 mg QM for 12 months followed by alendronate 70 mg QW significantly reduced the incidence of new vertebral fractures by 50% through 24 months, clinical fractures by 27% (primary endpoints), and nonvertebral fractures by 19% (key secondary endpoint), compared with alendronate alone (Saag et al, 2017). A nominally significant reduction of 38% in hip fractures was also observed in women in the romosozumab treatment group.

Refer to the specific section of the Investigator's Brochure for additional information related to the romosozumab clinical program and the pharmacology, efficacy and safety of romosozumab.

2.2.1 Pharmacology

In adults, the pattern of BMD increase with romosozumab shows large increases of BMD in the first 6 months and somewhat smaller albeit robust BMD increases in the second 6 months of the treatment period, resulting in increases in BMD after 12 months equivalent to those observed after 3 to 4 years of treatment with antiresorptives (McClung et al, 2014). However, in both animal models (Ominsky et al, 2012; Ominsky et al, 2017) and postmenopausal women (McClung et al, 2014), after an initial increase in serum bone formation markers, levels decline over a 2- to 9-month period with continued romosozumab treatment, suggesting a self-regulating effect. In addition to self-regulation, the effects of romosozumab on bone are reversible in adults. (Amgen Romosozumab Investigator's Brochure).

2.2.2 Pharmacokinetics

Pharmacokinetic data are available from 9 single-dose phase 1 studies, 3 multiple-dose phase 1 studies, 2 multiple-dose phase 2 studies, and 3 phase 3 studies in adult

populations. Overall, the PK properties of romosozumab have been well characterized and are similar to that of other IgG monoclonal antibodies.

Romosozumab exhibits nonlinear PK consistent with target-mediated drug disposition. Elimination of romosozumab likely occurs via 2 mechanisms: nonspecific catabolism (as for other IgGs) and saturable degradation of the romosozumab-sclerostin complex. The kidney and liver are not routes of IgG elimination, as IgG antibodies are too large to be filtered by the glomerulus, and cytochrome P450-mediated metabolism and biliary secretion do not play a role. No demographic or physical characteristic, as well as BMD status or prior treatment with alendronate, has been found to warrant an adjustment in dose.

The PK of romosozumab was evaluated in healthy subjects following administration of a range of single SC doses. Generally, C_{max} was observed within the first week after administration. Serum romosozumab concentrations declined with a mean half-life of approximately 11 to 18 days during the beta (plateau) phase and 6 to 7 days during the gamma (terminal) phase. The bioavailability of romosozumab was estimated to be 50% to 70% after SC administration of [redacted] to [redacted] mg/kg. Following administration of SC doses every [redacted] at [redacted] mg/kg for [redacted], accumulation based on mean C_{max} and AUC values following 3 doses was 20% to 36% more than exposure after the first dose. The mean effective $t_{1/2}$ was 12.8 days after 3 doses of [redacted] mg/kg. Approximately linear PK was observed when comparing C_{max} and AUC values following [redacted] and [redacted] mg/kg [redacted]. When multiple SC doses of romosozumab 70, 140, or 210 mg QM were administered to women with PMO or low BMD, steady state was generally reached by month 3 with minimal accumulation (< 2 fold) following multiple doses and approximately dose-proportional increase in PK exposure was observed in the dose range of 140 mg to 210 mg.

2.2.3 Preclinical Toxicology

This study is supported by a comprehensive package of nonclinical toxicology.

A panel of studies were conducted in adolescent rat and cynomolgus monkeys comparable to a 12-year-old human and older. Effects observed in the rat and monkey repeat-dose toxicology studies (14-day studies [30 to 300 mg/kg SC, 300 mg/kg IV]; 6-week study [50 mg/kg SC, rat only]; 1- and 6-month studies with 10- and 14-week recovery periods [3 to 100 mg/kg], respectively, in the rat and monkey) were either directly or indirectly related to the anticipated pharmacologic effects on bone. The

intended pharmacological effect of increased bone formation resulting in increased cortical and cancellous bone mass was observed with partial reversal of the bone mass effects at the end of the recovery period. Effects considered secondary to the pharmacological effects on bone included a mild regenerative anemia with compensatory extramedullary hematopoiesis and mild decrease in platelet number in rats, increased serum phosphorus in rats, and slightly lower serum calcium and phosphorus in monkeys; all of these effects were largely reversible during the recovery period. In safety pharmacology studies at doses up to 300 mg/kg IV, there were no neurobehavioral effects in rats or cardiovascular or respiratory effects in monkeys. In a lifetime pharmacology study in rats designed to assess the carcinogenic potential of romosozumab (initiated at 8 weeks of age comparable to a 10-yr-old human), the incidence of tumors was not increased in rats administered romosozumab at dose levels up to 50 mg/kg every week for up to 98 weeks.

Across four reproductive and developmental studies in rats, effects were limited to a slight increase in the incidence of reduced ventral processes on the 6th cervical vertebrae at 300 mg/kg with exposures at least 30-fold clinical at 210 mg QM. This single variation represents a delay in development in a skeletal process not found in humans. At 300 mg/kg, skeletal abnormalities (fused and extra digits) were seen in 1 of 75 litters (7 of 1021 fetuses/pups or 0.7% incidence) and were concluded to be unrelated to romosozumab based on the weight-of-evidence. At doses up to 300 mg/kg in rats, romosozumab had no effect on male or female fertility, or reproductive organ weights, and effects on postnatal development were limited to slight changes in bone mass or bone geometry.

2.3 Pediatric Risk Assessment

Romosozumab has demonstrated a favorable benefit-risk in postmenopausal women at high risk for fracture. The safety profile was evaluated in more than 14,000 subjects with the most common adverse reactions (≥ 1/10) being viral upper respiratory tract infection and arthralgia. Key safety risks for romosozumab include serious cardiovascular events of myocardial infarction and stroke, hypersensitivity reactions, hypocalcemia, and rare cases of osteonecrosis of the jaw (ONJ) and atypical femoral fracture (AFF). More detailed information about the known and expected benefits and risks may be found in the Romosozumab Investigator's Brochure.

Overall, pediatric subjects treated with romosozumab in this study are expected to have a risk profile comparable to that observed in adults. The potential risk of serious

cardiovascular adverse events of myocardial infarction and stroke is however not anticipated to occur in pediatric patients as such events are not typically observed in pediatric populations. Nonetheless subjects will be closely monitored and those at a high risk of cardiovascular disease (eg, familial hypercholesterolemia, valvular heart disease, or Kawasaki disease) will be excluded from this study.

Events of interest specific to the pediatric patient population include cranial hyperostosis and the effect on longitudinal bone growth, as well as effects on fetal development in those female subjects with reproductive potential, and are further discussed below.

- Cranial hyperostosis and nerve entrapment are observed in pediatric patients with hereditary disorders of sclerostin deficiency (sclerosteosis, van Buchem's disease) (Shah et al, 2015). Pharmacological inhibition of sclerostin may therefore carry a neurologic risk in children of any age. However, the risk is assumed to be higher among those with the fastest rate of skull growth. In patients with hereditary disorders of sclerostin deficiency, transient palsy of the seventh cranial nerve is the earliest neurologic complication and occurs during infancy, and bilateral facial paralysis is usually permanent by adulthood (Beighton et al, 1976). Hyperostosis or macroscopically thickened long bones and skull was observed in chronic toxicity studies in adolescent rats at exposures of romosozumab 38 to 93-fold greater than clinical exposure at 210 QM that partially reversed in recovery with no adverse consequences. Nonclinical data in adolescent and mature monkeys indicate the absolute increases in bone formation markers are higher in adolescent monkeys compared with adults, suggesting the immature growing skeleton may accrue more bone in response to romosozumab.

  Safety monitoring: To mitigate this risk, repeated facial nerve examinations are planned as part of the Schedule of Assessments, as a sensitive clinical approach to the early detection of signs of nerve entrapment. If treatment emergent facial nerve paresis or paralysis is suspected, referral to a neurology specialist for a complete cranial nerve examination will be performed, including audiologic and ophthalmoscopic assessment. In case of abnormal findings, the need for a CT or MRI scan of the cranial nerve tract should be further discussed and documented (Refer to Section 7.4.6).

- Longitudinal bone growth: For skeletally immature pediatric subjects, sclerostin inhibition could potentially result in increased longitudinal bone growth. Uncertainty remains regarding stimulation of bone formation in highly metabolically active bone tissue. Given the clinical manifestations of sclerostin deficiency in children (ie, tall stature), the higher rates of bone formation, and the presence of open growth plates, longitudinal bone growth is an event of interest to be considered with the use of romosozumab in pediatric population.

  Safety monitoring: Physical examinations will be performed on a regular basis throughout the study to monitor for possible detrimental skeletal changes.

- Fetal development: Skeletal abnormalities (fused and extra digits) were seen in 1 of 75 litters across the 4 reproductive and developmental studies at 300 mg/kg. Syndactyly is a feature of the sclerosteosis phenotype in humans and mice. The risk to the developing digits in the human fetus is low due to the timing of digit formation in the first trimester when placental transfer of immunoglobulins is limited. Romosozumab is not recommended for use in pregnancy. It is unknown whether romosozumab is present in human breast milk. The effects of romosozumab in breast-fed infants have not been assessed.

  Safety monitoring: if a study subject becomes pregnant, or if a pregnancy occurs in a female partner of a male study subject while on-study and up to 3 months after the last dose of study drug, the pregnant subject and fetus will be monitored during pregnancy through delivery for possible effects on the pregnancy outcome and health of the infant.

The following measures were adopted to minimize risk to the pediatric population in this study:

- Dose cohorts, starting with the lowest dose level, will be recruited so that adolescents will be enrolled first at each dose level before children at the same dose level.
- The small sample size of the study ensures limited exposure of romosozumab to adolescents and children until safety is confirmed.
- Subject exposure to romosozumab treatment will be limited to [redacted] doses, and subjects will be followed up for additional [redacted] after the last dose.
- Progression to a higher dose cohort and to a lower age cohort will only occur after a Dose Level Review Meeting confirmed the safety and tolerability of the lower dose (Section 6.2.1.2.1).
- Hypocalcemic patients will not be enrolled. Additionally, patients will be receiving calcium and vitamin D supplementation to minimize the risk of hypocalcemia.
- Subject eligibility criteria exclude subjects at increased risk for ONJ.
- Subjects at high risk for cardiovascular disease will be excluded from the study.
- Measures to reduce the risk of unintended fetal exposure are in place.

Volumes of blood withdrawn for analysis in association with clinical monitoring and X-ray exposure will be minimized as appropriate for this pediatric population (EU Ethical Considerations, 2016).

Additionally, in order to closely assess events of potential hypersensitivity reactions, all subjects will be monitored for at least 2 hours following the first and subsequent dosing of romosozumab. The monitoring observation will include assessment of hypersensitivity reactions.

Potential COVID-19 risks

- There are currently no data available that evaluated EVENITY® therapy in those who have received any of the COVID-19 vaccines
- The decision for the vaccination should be made according to the local guidance and standard of care. As stated in Section 6.8, vaccine administration is allowed during the study

Mechanism of action in relation to the COVID-19 risk:

- The available data does not suggest an effect of romosozumab on the immune system response
- Romosozumab binds and inhibits sclerostin. Nonclinical evaluations showed it is highly unlikely that inhibition of sclerostin by administration of romosozumab would be associated with an increased risk of infection, as sclerostin is not expressed in tissues or cells associated with immune system function, and romosozumab is not considered to be an immunomodulator.

Study population in relation to the COVID 19 risk:

- Pediatric patients of all ages can get COVID-19, although they appear to be affected less commonly than adults. In a systematic literature review (from January 1 through 18 March 2020), children accounted for 1 to 5 percent of diagnosed COVID-19 cases (Ludvigsson, 2020).
- There is no data on osteogenesis imperfecta (OI) and the risk of COVID-19 infection. Osteogenesis imperfecta does not affect the immune system. However, lung connective tissue is altered in all types of OI. The severity of symptoms and the risk of pulmonary problems is increased in people with short stature, abnormal chest shape, kyphoscoliosis, and vertebral or rib fractures. Thus, people with moderate to severe OI are more vulnerable to viral and bacterial respiratory infection of upper and lower airways, as well as lung problems, including pneumonia. Patients with OI have a higher risk of death from respiratory diseases (Turkalj et al, 2017).
- Subjects will be closely monitored and the potential impact of COVID-19 on these participants will be carefully considered when deciding to start or continue participation.

2.4 Non-Amgen Medicinal Product Background

Calcium and Vitamin D Background

Calcium and vitamin D are important in the formation of bone matrix and for its subsequent mineralization where calcium found as calcium hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$) provides bone and teeth tissues with their strength. Calcium and vitamin D are therefore considered key components of therapy in the management of osteoporosis (Ward et al, 2016; Dawson-Hughes et al, 2010;

Dawson-Hughes et al, 1990) and have been required as background therapies in all contemporary therapeutic trials in osteoporosis.

Furthermore, children with chronic diseases are more prone to calcium and vitamin D deficiency for a variety of reasons including malabsorption, limited sunlight exposure, nutritional restrictions and the use of medications (Mäkitie, 2013; Ward et al, 2016). Therefore, prevention of vitamin D and calcium deficiency should be routinely considered in those with chronic illnesses.

Transient mild hypocalcemia has been observed in patients receiving romosozumab. Hypocalcemia should be corrected prior to initiating therapy with romosozumab and patients should receive adequate supplementation of calcium and vitamin D while receiving romosozumab.

The recommended dietary allowance and tolerable upper intake level of dietary calcium recommended by the United States Institutes of Medicine (IoM) for children and adolescents aged 9 to 18 years on a western diet is 1,300 mg and 3,000 mg per day respectively. The recommended dietary allowance and tolerable upper intake level of dietary vitamin D for them is 600 IU and 4,000 IU per day (Ross et al, 2011; IoM, 2011; Ward et al, 2016). The daily supplementation required in this study, is safe, and represents commonly used and accepted doses for the management of children with osteoporosis.

2.5 Rationale

This study is part of a Pediatric Investigation Plan for romosozumab that was agreed upon with the European Medicines Agency. It will evaluate PK, PD and safety data (of romosozumab at [redacted] and up to [redacted] mg/kg, administered SC [redacted]) to support the design of the planned efficacy study in pediatric subjects with OI. To inform an appropriate dose level for the efficacy study, PK and PD results from this study may be combined with the data from adult romosozumab studies to perform a population PK/PD analysis.

Based on our understanding of the mechanism of action and available nonclinical and clinical data, children may benefit from treatment with romosozumab. Although the pathophysiology of OI includes the decreased production of normal collagen (type I OI) or the formation of abnormal collagen (type II-IV), increased bone turnover and decreased bone formation are both features of the disorder. Thus, this condition may be amenable to an agent, such as romosozumab, that increases bone formation and decreases bone resorption in adults. The magnitude of the treatment effect in children

with OI may be similar to, greater, or less than that observed in adults with PMO. Assessments of the effects of romosozumab will include changes in the bone formation marker P1NP, the bone resorption marker sCTX, and BMD by DXA. Both bone turnover markers (BTM), P1NP and sCTX, have been extensively studied during the clinical development of romosozumab, and their kinetics following different romosozumab dosing schemes have been thoroughly described for the adult osteoporotic population. BMD will be assessed by DXA. Dual-energy X-ray absorptiometry (DXA) is the preferred method for pediatric BMD measurements because of its speed, precision and low radiation exposure (Bachrach, 2007). Published data regarding pharmacologic treatment outcomes in pediatric OI have used DXA BMD assessments as the primary outcome (Ward et al, 2011; Bishop et al, 2013). In osteoporotic adults, BMD has been shown to improve with romosozumab treatment, with increases in BMD being detected as early as with 3 months of treatment.

No studies have been conducted to evaluate a potential difference in romosozumab pharmacokinetics between juvenile and adult animals because the relevance of such studies to human pharmacokinetic characteristics is not known. Published data for other monoclonal antibodies suggest that romosozumab PK are likely similar in pediatric and adult subjects (Fasanmade et al, 2011; Trippett et al, 2009; Glade Bender et al, 2008; Gordon et al, 2001). Based on the assumption of similar PK between pediatric and adult subjects, anticipated exposure to romosozumab in children was predicted using the population PK model developed with data from adult studies. The population PK model describes romosozumab PK following SC administration with parallel linear and nonlinear target mediated clearance. In order to predict romosozumab PK in children, that model structure was used when PK parameters, clearance and volume of distribution, were allometrically scaled by body weight using fixed exponents of 0.75 and 1.0, respectively.

Table 1. Anticipated Exposure in Children After 3 Doses of Romosozumab

Population	Dosage	Weight Range (kg)	Predicted Median AUC (µg/mL•day)	90% Interval of Predicted AUC (µg/mL•day)	Predicted Median C_{max} (µg/mL)	90% Interval of Predicted C_{max} (µg/mL)
Male and female	[redacted] mg/kg	10 – 90	80	43 – 146	9	5 - 16
	[redacted] mg/kg		411	223 - 718	37	21 - 65

children aged 5 to 17 years[a]	[redacted] mg/kg[b]		826	459 - 1411	71	41 - 119
PMO subjects aged 55 to 85 years[c]	210 mg	40 – 96	534	281 - 968	45	25 - 84

AUC = area under the curve; C_{max} = maximum-observed concentration; PMO = postmenopausal osteoporosis

[a] The lower weight range is based on the 50th percentile for the most severe osteogenesis imperfecta type that survives infancy (https://lpamrs.memberclicks.net/assets/documents/OI%20Weight.pdf); weight is capped at 90 kg so as not to exceed 5 injections at the [redacted] mg/kg dose level.

[b] If the pharmacokinetic exposure and/or pharmacodynamic effects are insufficient at [redacted] mg/kg and [redacted] mg/kg, a higher dose of [redacted] mg/kg may be explored

[c] Adult pharmacokinetic data are from Study 20060326.

The approved dose for the treatment of PMO is 210 mg SC QM for 12 monthly doses. However, in studies 20060220 and 20060221 subjects were administered higher doses or higher total exposures, supporting the exploration of the [redacted] mg/kg SC dose cohort if insufficient PK or PD responses are observed in the [redacted] or [redacted] mg/kg dose cohorts. Romosozumab was generally well tolerated at these higher doses or higher total exposures, and there were no safety findings which would preclude evaluating [redacted] mg/kg [redacted] in a pediatric population. For further details regarding the safety data in studies 20060220 and 20060221, please refer to the synopses of these studies:

Study 20060220: https://s3.amazonaws.com/ctr-amg-7161/20060220/b8b4cd2c-5e3d-4ef1-92cc-cdb2890d5fa4/afcb2e07-915d-43e7-86e9-bf9109b17798/01.42.03_Public_Results_Redacted_CSR_Synopsis_2008-11-26_20060220_Final_report-v1.pdf

Study 20060221: https://s3.amazonaws.com/ctr-amg-7161/20060221/c124c6b2-7f09-4f1f-b17a-fef8dcaaa468/97568b49-1e44-4e72-a147-5868798f930b/01.42.03_Public_Results_Redacted_CSR_Synopsis_2010-12-16_20060221_Final_report-v1.pdf

Romosozumab will be provided in a 3 cc sterile vial filled with 1 mL deliverable volume of 90 mg/mL romosozumab. The SC doses for this study are capped at 1.5 mL per injection. For doses split into multiple syringes, inject into separate sites. New injections will be given at least 1 inch from an old site. Pivotal phase 3 studies (20070337 and 20110142) were conducted with 70 mg/mL prefilled syringe (PFS) presentation. A bioequivalence study (20120277) for the 70 mg/mL PFS and the 90 mg/mL PFS presentations support use of the 90 mg/mL concentration (please refer to this link for the synopsis of the 20120277 study).

This study will be conducted per local regulatory and ethics committee/investigation review board requirements/guidelines, and data from this study will inform the selection of the dose for the subsequent pediatric safety and efficacy studies in OI patients.

2.6 Clinical Hypothesis

Romosozumab PK and PD, including the effects on BMD and BTM (P1NP and sCTX), will aid in the selection of the dose for the subsequent efficacy and safety study in pediatric subjects with OI. Romosozumab will be safe and well tolerated following multiple SC dose administrations in children and adolescents with OI.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multicenter, open-label, ascending multiple-dose study to evaluate romosozumab in ambulatory children (5 to less than 12 years of age) and adolescents (12 to less than 18 years of age) with OI.

At least 16 subjects will be enrolled into sequential cohorts 1 to 4 (4 subjects per cohort). All subjects will receive a total of [redacted] SC doses of romosozumab administered every [redacted]. Subjects in cohorts 1 (12 to less than 18 years of age) and 2 (5 to less than 12 years of age) will be administered romosozumab [redacted] mg/kg SC [redacted] Subjects in cohorts 3 (12 to less than 18 years of age) and 4 (5 to less than 12 years of age) will receive romosozumab [redacted] mg/kg SC [redacted] If the exposure and PD effects are determined to be insufficient at [redacted] and [redacted] mg/kg, at least 4 subjects each will enroll into cohorts 5 (12 to less than 18 years of age) and 6 (5 to less than 12 years of age) and be randomized to receive romosozumab [redacted] mg/kg SC [redacted] All subjects will receive daily supplementation with calcium and vitamin D.

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

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Up to 20 sites may participate in this study. Additional sites may be added. If necessary to achieve enrollment goals.

Enrollment is competitive, sites that do not enroll subjects within 4 months of site activation may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. Approximately 8 subjects (5 to less than 12 years of age) and 8 subjects (12 to less than 18 years of age) will be enrolled in cohorts 1 to 4.

In addition, 4 subjects (5 to less than 12 years of age) and 4 subjects (12 to less than 18 years of age) may be enrolled in the optional cohorts 5 and 6 if the exposure and PD effects are insufficient at [redacted] and [redacted] mg/kg doses.

3.4 Replacement of Subjects

In the event subjects are enrolled, but are withdrawn prior to the first dose of investigational product administration, a replacement subject may be enrolled.

Additionally, subjects who are withdrawn from the study (see Section 8.3.2) with insufficient duration of follow-up after administration of study drug may be replaced at the discretion of Amgen in consultation with the investigator or his or her designee.

The new subject will receive the identical treatment as the replaced subject, but will be assigned a replacement number associated with this new record. All data from the replaced subjects will be captured, identified, and kept in the clinical trial database.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The estimated study duration for each subject is approximately 7 months. This includes a 35-day screening period prior to the first dose of investigational product and an on-study period of approximately 169 days. If there is a clinically significant clinical or laboratory abnormality in need of monitoring, subjects will be followed until resolution of the abnormality or until the subject is considered clinically stable in the opinion of the principal investigator.

3.5.2 End of Study

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

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

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

4. SUBJECT ELIGIBILITY

4.1 Inclusion Criteria

101. Subject's legally acceptable representative has provided informed consent and the subject has provided written assent based on local regulations and/or guidelines prior to initiation of any study-specific activities/procedures

102. Ambulatory male or female children 5 to less than 12 years of age (cohorts 2, 4, and 6) or adolescents 12 to less than 18 years of age (cohorts 1, 3 and 5) upon entry into screening

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

4.2 Exclusion Criteria

201. History of an electrophoresis pattern inconsistent with type I to type IV OI

202. History of known mutation in a gene other than type I collagen alpha 1/type I collagen alpha 2 (COL1AI/COL1A2) causing OI or other metabolic bone disease

203. History of congenital dislocation of the radial head, interosseous membrane calcification, or exuberant callus formation

204. History of osteomalacia or rickets

205. Body weight less than 10 kg or greater than 90 kg

206. History of other bone diseases that affect bone metabolism (eg, osteoporosis pseudoglioma syndrome, idiopathic juvenile osteoporosis, osteopetrosis, hypophosphatasia)

207. History of Kawasaki disease, rheumatic myocarditis, ischemic cardiomyopathy, inherited cardiomyopathies, nephrotic syndrome, familial hypercholesterolemia, stroke, or any thromboembolic disorder

208. Evidence of untreated or unhealed oral cavities or oral infections

209. Unhealed or planned invasive dental or tooth procedure; removal of baby teeth is acceptable and not considered an invasive dental procedure

210. Unhealed fracture as defined by orthopedic opinion

211. Osteotomy, rodding surgery or spinal fusion surgery within 5 months prior to screening, or not yet healed per orthopedic surgeon

212. Any planned major surgery, including skeletal surgery (eg, rodding surgery, spinal surgery) within the next 6 months from day 1 that would interfere with study procedures or would require missing of any IP

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

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

215. History of long QT syndrome

216. History of malignancy

217. History of any solid organ or bone marrow transplant

218. Positive blood screen for hepatitis B surface antigen (HbsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody (HepCAb), human immunodeficiency virus (HIV) -1 or -2 antibody

219. History of hyper- or hypothyroidism, unless subject is on stable therapy > 6 months and has supporting laboratory documentation within 6 months prior to or at screening indicating normal serum thyroid-stimulating hormone [TSH] value

220. Evidence of any of the following:

- Current hyper- or hypoparathyroidism (parathyroid hormone outside the normal range)
  - Renal disease: Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (calculated by the bedside Schwartz equation at screening)

    $$eGFR\ (mL/min/1.73\ m^2) = 0.413\ X\ (height/serum\ creatinine)$$

    1. (Height is in centimeters, and serum creatinine is in mg/dL)

  - Current hypocalcemia (albumin-adjusted serum calcium < LLN of the laboratory's reference range) or hypercalcemia (albumin-adjusted serum calcium > ULN of the laboratory's reference range) at the time of screening. Serum calcium levels may be retested once in case of an elevated serum calcium level within 1.1 x ULN of the laboratory's reference range.
  - Serum phosphorous < LLN
  - Vitamin D insufficiency, defined as 25OHD levels < 20 ng/mL; vitamin D repletion will be allowed and subjects may be retested.
  - Aspartate aminotransferase (AST), alanine aminotransferase (ALT) > 1.5 x upper limit of normal (ULN)
  - Total bilirubin > 1.5 x ULN (subjects with Gilbert syndrome are eligible)

221. Prior treatment with:

- romosozumab or other anti-sclerostin antibody

- fluoride or strontium for bone disease
- parathyroid hormone (PTH) or PTH derivatives within 12 months prior to screening
- Denosumab within 12 months prior to first dose of romosozumab
- zoledronic acid within 6 months prior to first dose of romosozumab
- oral bisphosphonates or intravenous bisphosphonates other than zoledronic acid if the first dose of romosozumab would be before their next scheduled bisphosphonate dose would have been given

222. Subject unwilling to stop IV or oral bisphosphonate prior to the first dose of IP

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

- Systemic glucocorticoids (≥ 5.0 mg prednisone equivalent/day for more than 10 days) within 3 months prior to screening. Topical and inhaled glucocorticoids will be allowed
- Growth hormone (subjects on stable dose of growth hormone for at least 3 months prior to screening will be allowed)
- Calcitonin
- Other bone active drugs including anticonvulsants (except gabapentin and benzodiazepines) and heparin
- Chronic systemic ketoconazole, androgens (except subjects who have received testosterone therapy for physiologic replacement in the setting of documented hormonal deficiency), adrenocorticotropic hormone (ACTH), cinacalcet, aluminum, lithium, protease inhibitors, gonadotropin-releasing hormone agonists

224. Currently receiving treatment in another investigational drug study, or less than 30 days or 5x the half-life, whichever is longer, since ending treatment on another investigational drug study(s), or current or planned participation in a clinical trial that would preclude compliance with study requirements

225. Known intolerance to calcium or vitamin D supplements

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

227. History of alcohol or drug abuse

228. Unwilling or unable to abstain from nicotine or tobacco containing products or drug substances of abuse throughout the screening period and for the duration of the study

229. Females of reproductive potential who are unwilling to practice an acceptable method(s) of highly effective birth control while on study through day 169 (for subjects who remain on study through completion) or for 3 months after last dose of IP(for subjects who withdraw prior to end of study). Acceptable methods of highly effective birth control are described in Section 6.9.
230. Females with a positive pregnancy test, or who are currently pregnant or planning to become pregnant or who are lactating/breastfeeding while on study through day 169 (for subjects who remain on study through completion) or for 3 months after last dose of IP (for subjects who withdraw prior to end of study)
231. Subject will not be available for protocol-required study visits
232. Subject's parent or legal representative that, in the opinion of the investigator, may present with compromised ability to give written permission for informed consent
233. Less than 2 evaluable vertebrae by DXA evaluation in the region of interest, L1-L4, as confirmed by the central imaging laboratory.
234. Subject has known sensitivity to any of the products or components to be administered during dosing
235. Subject previously has enrolled in this study
236. Clinically significant valvular heart disease based on local echocardiogram (ECHO) results.

5. SUBJECT ENROLLMENT

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

Subjects who reach 18 years of age (or legal age in the country indicated) during the study will need to provide informed consent by personally signing and dating the ICF.

Adverse events are to be collected for a subject once they are enrolled in the study. A subject is considered enrolled when the investigator confirms that the subject has met all eligibility criteria (both screening and day 1 pre-dose assessments). The investigator is to document this decision and date in the subject's medical record and in/on the enrollment case report form (eCRF).

Each subject who enters into the screening period for the study (defined as when the informed consent and subject assent forms are duly signed) receives a unique subject identification number before any study-related activities/procedures are performed.

The subject identification number will be assigned using interactive response technology (IRT). This number will be used to identify the subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

The subject identification number will be 11 digits: the first 3 digits are the protocol identifier (227), the next 5 digits consist of the 2-digit country code (66, US) and the 3-digit study-specific site number (001), and the last 3 digits are assigned in incremental order within each site as subjects are screened starting at 301. Thus, the identification for the first subject screened at site 001 in the US will be [redacted], the identification number for the second subject screened at site 001 will be [redacted], and so forth.

6. TREATMENT PROCEDURES

6.1 Classification of Product

The Amgen investigational products used in this study is romosozumab

The other protocol-required products used in this study include: calcium and vitamin D.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of romosozumab.

6.2 Investigational Product

All investigational product (IP) romosozumab will be administered at the research facility by a qualified staff member.

A physician must be available at the time of administration of Investigational Product.

6.2.1 Amgen Investigational Product – Romosozumab

Romosozumab for SC will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Romosozumab will be provided in a 3 cc sterile vial filled with 1 mL deliverable volume of 90 mg/mL romosozumab. The SC doses for this study are capped at 1.5 mL per injection. Doses split into multiple syringes will be injected into separate sites. New injections will be given at least 1 inch from an old site.

6.2.1.1 Dosage, Administration, and Schedule

Amgen will supply romosozumab to study sites.

Subjects will receive romosozumab via SC injection on days [redacted], according to the Schedule of Assessments (Table 6). At the end of the initial [redacted] treatment period, all subjects will be followed and monitored for safety for an additional [redacted] Romosozumab will be administered as a weight-based dose determined based on each subject's weight assessed at the time of dosing.

The date and time of IP administration will be recorded on the eCRF.

The planned dose levels and cohorts are described in the table below.

Table 2. Planned Dose Cohorts

Cohort #	Age Group (years of age)	Dose[a]	Dosing Day	N
1	12 to less than 18	[redacted]		4
2	5 to less than 12			4
3	12 to less than 18			4
4	5 to less than 12			4
5 (optional)	12 to less than 18			4
6 (optional)	5 to less than 12			4

[a] All doses will be administered subcutaneously

6.2.1.2 Dose-cohort Study Escalation and Stopping Rules

The planned doses of romosozumab are shown in Table 2. IP will be administered on day [redacted], day [redacted] and day [redacted] following all required pre-dose procedures.

The dosing schedule is described by a schema in the protocol synopsis.

6.2.1.2.1 Dose Level Review Meetings

A dose level review meeting (DLRM) will be held to review data and monitor safety before escalation to the next higher dose or expansion to the younger age cohort. The DLRT members will be composed of, at a minimum, the investigators actively enrolling subjects at the time of the meeting (ie, have subjects in screening or already enrolled), the Amgen Medical Monitor, and Amgen Global Safety Officer or designated safety scientist, Amgen Clinical Research Study Manager or designee, and biostatistics representative or designee. Additional members may be added as needed (eg, PK scientist). The DLRT voting members include the principal investigator or designee, Amgen Medical Monitor and Amgen Global Safety Officer or designee.

The DLRT voting members are responsible for dosing recommendations, which may include escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), de-escalation to a lower dose; continuation, delay, or termination of dosing; or repetition or expansion of a cohort. Clear stopping rules will be followed, and ad hoc DLRMs will be held if necessary. All available study data, including demographics, medical history, concomitant medications, adverse events, electrocardiograms (if applicable), vital signs, and clinical laboratory test results will be reviewed.

The Amgen Medical Monitor will review data on an ongoing basis throughout the duration of study.

Investigators who are not actively enrolling subjects at the time of the DLRM will not participate in the DLRM. They will be informed of the recommendations of the DLRM.

6.2.1.2.2 Dose Stopping Rules

Determination of the severity of adverse events will be based on the **Severity Intensity** Scale **for Adverse Events**.

The DLRT will recommend stopping or modifying dosing if suspected adverse drug reactions, changes in vital signs, electrocardiogram (ECG), or clinical laboratory results are observed and these changes pose a significant health risk. In addition, dosing will be stopped or modified if any of the stopping rules shown in Table 3 are met. The Amgen Medical Monitor will review data in an ongoing basis, may suspend dosing and convene a DLRM at any time based on emerging safety data.

Clinically or medically significant suspected adverse drug reactions, and serious adverse events considered to be related to study procedures will be followed until resolved or considered stable.

The study may be terminated at any point at the discretion of the sponsor.

Table 3. Cohort Dose Stopping Rules

Scenario	Action
Any occurrence of a **Severity Intensity** Scale **for Adverse Events** moderate suspected adverse drug reaction of the same system organ class (eg, hepatobiliary, cardiovascular) in 2 or more subjects in the same cohort	• Stop dosing additional subjects and convene DLRM (if event occurs outside of the regularly scheduled DLRM) • Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance • Based on the DLRM vote, one of the following decisions may be made: o stop enrollment of the cohort (if applicable) o resume enrollment of the cohort as planned o continue enrollment of the cohort at a lower dose o expand the cohort at the same dose o continue enrollment of the study at a lower dose o upon unanimous vote escalate to an intermediate dose (a dose lower than the next planned dose) o upon a unanimous vote escalate to the next planned dose
Any occurrence of a **Severity Intensity** Scale **for Adverse Events** severe suspected adverse drug reaction	• Stop dosing additional subjects and convene DLRM (if event occurs outside of the regularly scheduled DLRM) • Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance • If the adverse event is determined by a majority vote of the DLRT to be related to study drug and clinically or medically significant, recommend that no further doses should be administered at this dose and no dose escalation should proceed. Recommend that enrollment of the study continue at a lower dose or a lower dose cohort may be added to the study. • Otherwise based on majority vote of the DLRT, one of the following decisions may be made: o resume enrollment of the cohort as planned o continue enrollment of the study at a lower dose or add a lower dose cohort to the study o expand the cohort at the same dose

DLRM = dose level review meeting; DLRT = dose level review team

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

Romosozumab will be administered as a weight-based dose determined based on each subject's weight assessed at the time of dosing. Romosozumab will be administered at a dose of [redacted] mg/kg, [redacted] mg/kg or up to [redacted] mg/kg body weight.

If a subject misses a scheduled dose of IP during a study visit, then he/she should return to the clinic to receive the missed dose within the visit window allowed for that particular visit (see Section 7.2). The clinical monitor should be contacted for specific instructions if a subject cannot receive his/her dose within the allowed visit window.

If a subject discontinues IP early, the investigator is to discuss with the subject the appropriate processes for discontinuation and the option to continue study assessments until day 169. The investigator must document the change to the Schedule of Assessments and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

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

6.3 Other Protocol-required Therapies

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

All subjects are required to take daily supplements of 30-50 mg/kg (not to exceed 1000 mg calcium) and at least 800 IU vitamin D for the duration of the study to minimize the risk of hypocalcemia.

If a subject becomes hypercalcemic over the course of the study, the calcium and/or vitamin D supplementation may be discontinued until serum calcium concentrations has returned to the normal range.

If a subject becomes hypocalcemic over the course of the study, the calcium and/or vitamin D supplementation may be increased, per medical judgment of the investigator.

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

The dose, start date, stop date, and frequency for calcium and vitamin D are to be recorded on the eCRF. The reason for dose change of calcium and/or vitamin D supplementation is to be recorded on the eCRF.

6.4 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], AST, ALT, total bilirubin) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen IP or other protocol-required therapies as specified in the Guidance for Industry Drug-induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.4.1 Criteria for Permanent Withholding of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

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

- Total bilirubin > 2x 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 total bilirubin values include, but are not limited to:
  - Hepatobiliary tract disease
  - Infectious hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
  - Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
  - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - Alpha-one antitrypsin deficiency
  - Alcoholic hepatitis
  - Autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - Nonalcoholic fatty liver disease including steatohepatitis (NASH)
  - Non-hepatic causes (eg, rhabdomylosis, hemolysis)

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

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

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

Baseline AST or ALT value	AST or ALT Elevation
Any	> 8x ULN at any time
Any	> 5x ULN but < 8x ULN for ≥ 2 weeks
Any	> 5x ULN but < 8x ULN and unable to adhere to protocol 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, and jaundice).

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

Investigational product and other protocol-required therapies, as appropriate, should be withheld pending investigation into alternative causes of DILI. If IP is withheld, the subject is to be followed according to recommendation in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated total bilirubin is discovered and the laboratory abnormalities resolve to normal or baseline.

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

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

If signs or symptoms recur with rechallenge, then IP and other protocol-required therapies, as appropriate should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.4.1) should never be rechallenged.

6.5 Concomitant Therapy

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

The use of prescribed therapies (ie, bisphosphonate) will be allowed to manage adverse event (ie, hypercalcemia), if deemed necessary by the investigator.

Concomitant therapies are to be collected from informed consent through the end of study. Collect therapy name, indication, dose, unit, frequency, and route, start date, and stop date. Concomitant medications will not be collected after the end of study (EOS) visit for any subjects with additional safety follow-up.

Prior medication (medication taken 24 months prior to subject enrolling on study) will also be recorded on the concomitant eCRF.

6.6 Alcohol, Tobacco, and Drug Substances of Abuse Restrictions

Subjects are not permitted to consume any alcohol within 24 hours prior to a study visit, including screening.

Subjects are not permitted to use nicotine or tobacco containing products or drug substances of abuse throughout the screening period and for the duration of the study.

6.7 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 **or** 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.**

Any product complaint associated with an investigational product supplied by Amgen are to be reported.

6.8 Excluded Treatments and/or Procedures During Study Period

All medications listed in the exclusion criteria, shown in the table 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.

Table 4. List of Proscribed Therapies

aluminum	calcium chelators	parathyroid hormone (or a derivative)
anabolic steroids	chemotherapeutics	progestins, when used as monotherapy
androgens[a]	chronic heparin use (> 7 days)	prolonged glucocorticoid therapy at a prednisone equivalent dose of ≥ 5.0 mg/day (tapering glucocorticoid courses of ≤ 1 month duration are permitted regardless of dose; inhaled or topical glucocorticoids are permitted)
anticonvulsants (gabapentin and benzodiazepines are allowed)	cinacalcet	
any investigational agents other than study drug	blood citrated products	
aromatase inhibitors	fluoride	
biologics (except for insulins and vaccines)	gonadotropin-releasing hormone agonists	
bisphosphonate[b]	growth hormone (unless stable for at least 3 months prior to screening)	protease inhibitors
calcitonin	immunosuppressants	strontium
	lithium	tibolone

[a] Except subjects who are receiving testosterone therapy for physiologic replacement in the setting of documented hormonal deficiency
[b] Will be allowed to manage adverse event (ie, hypercalcemia), if deemed necessary by the investigator

6.9 Contraceptive Requirements

Pregnant or breastfeeding females and females planning to become pregnant should not participate in this study. Females of reproductive potential, must use an acceptable method of highly effective birth control while on study through day 169 (for subjects who remain on study through completion or for 3 months after the last dose of study drug (for subject who withdraw prior to end of study).

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

Females are considered of reproductive potential if they have had menarche. Female subjects who have had menarche and those that experience menarche whiles on study will need to have pregnancy testing.

Female subjects of reproductive potential must agree to use highly effective methods of contraception (as described in the table below) and to continue this practice while on study through day 169 for subjects who remain on study through completion) or for 3 months after the last dose of investigational product (for subjects who withdraw prior to end of study).

Table 5. Acceptable Contraceptive Methods (Highly Effective) for Female Subjects

- Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, injections, intravaginal, or transdermal)
- Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or 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 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).

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

If a pregnancy occurs in a female partner of a male subject, while the subject is in the study, report the pregnancy to Amgen as specified below. In addition to reporting pregnancy during the study, investigators should monitor for pregnancies that occur through 3 months after the last dose with investigational product.

The pregnancy should be reported to Amgen Global Patient Safety **immediately and no later than** 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

6.9.1 Unacceptable Methods of Birth Control for Female Subjects

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

Female subjects of reproductive potential must receive pregnancy prevention counseling and be advised of the risk to fetus if they become pregnant during the study through day 169 (for subjects who remain on study through completion) or for 3 months after the last dose of investigational product (for subjects who withdraw prior to end of study).

6.9.2 Male Participants

Male participants are not required to use birth control during treatment with romosozumab.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 6. Schedule of Assessments

Activity[a]	Screening	Treatment												Follow-up	EOS[j]
Study Day	**-35 to -1**														
Time (in hours)[b]															
Visit Windows				**± 2 days**	**± 3 days**		**± 3 days**	**± 3 days**		**± 2 days**	**± 3 days**			**± 7 days**	
General Assessments															
Informed Consent	X														
Medical History	X														
Physical Examination	X	X							X				X		X
Facial Nerve (Cranial Nerve VII) Examination		X							X				X		X
Vital Signs (HR, RR, TEMP)	X	X				X			X		X	X	X	X	X
Weight	X	X				X			X						X
Height	X														X
12-lead ECG	X			X		X									X
Echocardiogram[i]	X														
Concomitant medications	←	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Adverse Event Recording		←	—	—	—	—	—	—	—	—	—	—	—	—	→
Serious Adverse Event Recording	←	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Central Laboratory Assessments															
Clinical Chemistry with calcium, phosphorous, and magnesium levels	X	X		X		X			X		X		X	X	X
25(OH) Vitamin D Level	X														
iPTH	X	X		X		X			X				X	X	X
Clinical Hematology	X	X				X			X				X		X
HIV, HBcAb, HBsAg, and HepCAb	X														

Table 6. Schedule of Assessments

Activity[a]	Screening	Treatment											Follow-up	EOS[j]
Study Day	**-35 to -1**													
Time (in hours)[b]														
Visit Windows				± 2 days	± 3 days		± 3 days	± 3 days		± 2 days	± 3 days		± 7 days	
Local Laboratory Assessments														
Pregnancy Test (Serum at screening, Urine dipstick method all other timepoints)[c]	X	X				X			X					X
Alcohol and drug testing[d]	X													
Imaging Assessments														
DXA (AP lumbar spine)	X											X		X
Dosing														
Dispensation of calcium and vit D			X				X			X		X	X	
[redacted][n]														
Pharmacokinetic and Other Blood Samples														
Serum PK		X		X	X	X			X		X	X	X	X	X
Bone Turnover Markers (sCTX and P1NP)[e]		X		X	X	X			X		X	X	X	X	X
Antiromosozumab Antibody		X			X	X							X		X
Telephone Safety Assessments															
Telephone Safety Assessment[g]								X							

ECG = echocardiogram; EOS = end of study; HbsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HepCAb = hepatitis C antibody; iPTH = intact parathyroid hormone; HIV = human immunodeficiency virus; HR = heart rate; P1NP = procollagen type 1 N-terminal propeptide; PK = pharmacokinetics; sCTX = serum type I collagen C-telopeptide; RR = respiratory rate; TEMP = temperature

[a] The investigator may utilize investigator's staff or a qualified home healthcare service provider to provide such services at the subject's home as appropriate per institutional policies, local law and regulations, and in accordance with the study laboratory manual. Home visits can be performed for visit days 8, 15, 64, 71, and 113.
[b] Relative to study drug administration on day 1
[c] Pregnancy test will be performed for female subjects that have had menarche and for those that experience menarche while they are on the study. Screening pregnancy test will use serum samples, but all other pregnancy assessment will be done using urine samples.
[d] At PI discretion according to local guidance.
[e] sCTX and P1NP should be taken approximately the same time (± 1 hour) of day 1 collection time.

[redacted]

[g] PI or designee should perform telephone safety assessment on day 43 (± 3 days), the assessment should include recording any adverse or serious adverse event and any concomitant medications.
[h] Injection site reactions (ISR) should be evaluated at every visit, approximately 20 to 30 minutes after administration of investigational product. Confirmed ISR should be appropriately reported as adverse events.
[i] Echocardiogram will be performed only at screening if subject does not have prior echocardiogram performed in the last 6 months.
[j] If subject discontinues from study, the EOS visit will be the same as the follow-up visit**. After end of study, serious adverse events, regardless of causality, will be reported to Amgen. Please refer to Section 9.2.3 for additional details.**

7.2 General Study Procedures

Study tests and procedures will be performed only after written informed consent and subject assent (as applicable by local law) is obtained. During the study, every effort should be made to conduct study procedures as described in the Schedule of Assessments (Table 6). The investigator may utilize investigator's staff or a qualified home healthcare service provider to provide such services at the subject's home as appropriate per institutional policies, local law and regulations, and in accordance with the study lab manual.

Any missed visits, tests not done, and examinations not conducted must be reported as such on the eCRFs.

In the event that multiple procedures are required to be conducted at the same time, ECG and vital sign assessments should be performed before blood samples are drawn.

On-study bone turnover markers (BTM: sCTX and P1NP) samples should be collected approximately at the same time (± 1 hour) of day 1 collection time.

All blood samples should be collected at the same time at each visit.

Blood draws and safety assessments on dosing day should be performed before IP administration.

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

Acceptable windows for visits and PK and BTM sample collections:

± 2 days for days 8 and 64

± 3 days for days 15, 29, 57, 71, and 85

± 7 days for days 113 and 169/EOS

Laboratory Assessments

For a complete listing of laboratory test panels and analytes, please refer to Section 7.4.12.

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

7.2.1 Screening

After informed consent and subject assent are obtained, screening procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 6). 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 the Subject Enrollment Case Report Form. Each subject who enters the screening period for the study will receive a unique subject identification number before any study-related activities/procedures are performed. The subject identification number must remain constant throughout the entire clinical study; will be assigned using IRT. 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.

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

The following procedures are to be completed during the screening period:

- Confirmation that the Informed Consent Form and Assent form have been signed
- Demographic data including sex, date of birth, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.
- Medical history
- Physical examination as per standard of care
- Vital signs (ie, heart rate, respiration rate, and temperature)
- Weight and height
- ECG
- Laboratory assessments including clinical chemistry, hematology, calcium, phosphorous, magnesium, and 25(OH) vitamin D level, iPTH, and serology for HIV, HBcAB, HbsAg, and HepCAb
- Pregnancy test (Serum method)
- DXA assessments of the anteroposterior (AP) lumbar spine
- Echocardiogram (will be performed only if subject do not have prior echocardiogram performed in the last 6 months)
- Serious adverse event reporting
- Prior and concomitant medication
- Alcohol and drug testing (at Principal Investigator's discretion according to local guidance)

7.2.2 Rescreening

Re-screening of subjects is acceptable upon discussion with and approval by the Amgen Medical Monitor. A new ICF must be signed unless it has been < 35 days since the previous ICF signature was obtained. Subjects may be rescreened only once.

Subject with a 25-OH vitamin D level < 20 ng/mL can be repeated and retested at the investigator's discretion.

Repeat Assessments:

Reassess all the screening procedures, except for DXA and serology for HIV, hepatitis B virus, and hepatitis C virus, in subjects who are rescreened > 35 days, but < 6 months after screen failure.

Reassess all the screening procedures in subjects who are rescreened ≥ 6 months after screen failure.

7.3 Treatment Period

The following procedures will be completed during the [redacted] treatment period at the times designated in the Schedule of Assessments (Table 6).

- Physical Examination as per standard of care
- Bilateral facial nerve function examination (cranial nerve VII)
- Vital signs (ie, heart rate, respiration rate, and temperature)
- Weight
- ECG
- Laboratory assessments including chemistry with calcium, phosphorus, magnesium, iPTH levels, and hematology
- Pregnancy test (urine dipstick method), pre-dose performed on days of dosing for female subjects that have had menarche and those that experience menarche while they are on the study, testing will be performed at next scheduled assessment following first menstrual period.
- Adverse event and serious adverse event reporting
- Documentation of concomitant medications
- Dispensation of calcium and vitamin D
- Collection of serum PK sample
- Bone turnover markers (sCTX and P1NP)
- Collection of anti-romosozumab antibody sample
- IP administration (day [redacted] day [redacted] and day [redacted]

If any subject stops treatment (ie, due to an adverse event), the subject will be asked to continue to complete protocol-required visits for safety monitoring as determined by the

investigator in consultation with the Amgen Medical Monitor and Amgen Global Safety Officer.

7.3.1 Follow-up Visit(s) and End of Study Visit

Subjects will return to the clinic for follow-up visits on study days 64, 71, 85, and 113. End of study visit will occur on day 169/EOS.

Refer to the Schedule of Assessments (Table 6) for additional details.

- Physical Examination as per standard of care
- Bilateral facial nerve function examination (cranial nerve VII)
- Vital signs (ie, heart rate, respiration rate, and temperature)
- Weight and height
- ECG
- Laboratory assessments including chemistry with calcium, phosphorous, magnesium, iPTH levels, and hematology
- DXA assessments of the AP lumbar spine (DXA will not be performed on study day 113)
- Pregnancy test (urine dipstick method)
- Adverse event and serious adverse event reporting
- Documentation of concomitant medications
- Dispensation of calcium and vitamin D
- Collection of serum PK sample
- Bone turnover markers (sCTX and P1NP)
- Collection of anti-romosozumab antibody sample

If the subject discontinues the study prior to the day 169 visit, a follow-up visit will occur within 30 days of the last dose of IP or subject's last visit. All procedures outlined for the end of study visit, day 169, will be performed during this follow-up visit with the following exception: DXA scans will only be performed if $>$ 30 days have elapsed since the previous DXA assessment.

7.4 Description of Study Procedures

7.4.1 Data Collection

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

7.4.2 Informed Consent and Assent

After ICF and assent have been obtained, all screening procedures and tests establishing eligibility will be performed within 35 days of day 1. Screening procedures are summarized in the Schedule of Assessments (Table 6).

7.4.3 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety.

7.4.4 Medical History

The investigator or designee will complete a general medical/surgical history collected prior to enrollment and up to the time of enrollment and will be recorded on the eCRF. Medical history will include information on the subject's past and concurrent medical conditions. Fracture history must be recorded regardless of the time frame.

7.4.5 Physical Examination

The investigator or qualified designee will perform a complete physical examination (excluding breast, genital and rectal examination) at the time points specified in the Schedule of Assessments (Table 6).

7.4.6 Facial Nerve Examination

Facial nerve (cranial nerve VII) examination will be performed at time points specified in the Schedule of Assessments (Table 6). Facial nerve function will be assessed clinically by facial symmetry inspection at rest, followed by assessment of the symmetry of specific facial movements: raising eyebrows, closing the eyes, blowing out the cheeks, smiling, pursing and closing the lips. The examination aims to detect the early presence of a peripheral nerve lesion, therefore subjects should be evaluated for asymmetries affecting the entire side of the face.

If treatment emergent facial nerve paresis or paralysis is suspected, or medical history supports a suspected treatment emergent cranial nerve compromise (eg, new paresthesia in a cranial nerve territory, or reduction in auditory acuity), further doses of investigational product should be stopped, the Amgen Medical Monitor should be informed, and the subject should be referred to a neurology specialist for a complete cranial nerve examination, including audiologic and ophthalmoscopic assessment. In case of abnormal findings, the need for a CT or MRI scan of the cranial nerve tract should be further discussed and documented.

7.4.7 Height and Weight

Height measurements will be performed in the standing position without shoes, unless it is not possible to do so. In instances where standing height cannot be measured, measurement of recumbent height will be allowed.

Height and weight measurements (in kg and without shoes) will be obtained at time points specified in the Schedule of Assessments (Table 6).

7.4.8 Vital Signs

Vital signs will include temperature, respiration rate and heart rate obtained in the sitting position after the subject has been sitting quietly for at least 5 minutes. The position and temperature location selected for a subject should be the same throughout the study and documented on the vital sign eCRF. Abnormal measurements may be repeated at the discretion of the investigator and must be reported on the corresponding unscheduled eCRF page.

7.4.9 Pregnancy Test (Female Subjects Only)

Pregnancy tests will be performed from serum sample to be collected at screening and urine samples collected pre-dose on days [redacted] and 169/EOS in all female subjects who have had menarche and those that experience menarche while on study, testing will be performed at next scheduled assessment following menstrual period. A negative pregnancy test must be confirmed prior to administration of study drug at all scheduled visits (as applicable). Female subjects who experience menarche while they are in the study will be subject to the pregnancy testing as specified in the Schedule of Assessments (Table 6) starting with the next scheduled assessment following their first menstrual period.

Female subjects who become pregnant during the study will be followed for safety until end of study. A Pregnancy Notification Worksheet (Appendix C) will be completed for subjects with a positive test result at any point after providing informed consent and assent.

7.4.10 Dual-energy X-ray Absorptiometry (DXA) Assessments

Bone density of the lumbar spine will be assessed by DXA at time points specified in the Schedule of Assessments (Table 6).

Only General Electric Lunar or Hologic bone densitometers will be allowed for this study. The same DXA machine must be used for all study procedures for a particular subject.

Lumbar spine scans should include L1 through L4. At least 2 lumbar vertebrae from L1-L4 must be evaluable by DXA.

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

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

7.4.11 Electrocardiogram

12-lead ECGs will be performed using standard ECG machine at time points specified in the Schedule of Assessments (Table 6). A single ECG will be performed at each time point. Subject must be in a semi-recumbent position in a rested and calm state for at least 5 minutes before the ECG assessment is conducted. If the subject is unable to be in the semi-recumbent, the subject should be in the most recumbent position possible. The ECG must include the following measurements: RR, QRS, QT, QTc, and PR intervals.

The investigator will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

7.4.12 Echocardiogram

Echocardiogram will be performed to evaluate subject's eligibility for the study at screening. Echocardiogram conducted within the past 6 months prior to the screening is acceptable to determine the subject's eligibility according to this criterion. Patients with clinically significant valvular heart disease will be excluded from the study. The test can be repeated if clinically indicated by the investigator.

7.4.13 Clinical Laboratory Assessments

All blood samples will be obtained by venipuncture before IP administration. See Table 9 for approximate sample volumes and blood collections for the study.

Blood will be obtained at the time points outlined in the Schedule of Assessments (Table 6). The date and time of blood collection will be recorded in the subjects' medical records.

7.4.13.1 Clinical Chemistry

The clinical chemistry tests listed below will be performed:

Table 7. Chemistry Panel

albumin	blood urea nitrogen	Sodium
alkaline phosphatase (ALP)	creatinine	total protein
ALT (SGOT)	creatine kinase	glucose
AST (SGPT)	chloride	25-OH vitamin D
bicarbonate (HCO_3)	magnesium	iPTH
direct bilirubin	phosphorous	calcium
total bilirubin	potassium	albumin-corrected calcium

Samples will be analyzed by the central laboratory. Refer to the Central Laboratory Manual for instructions on how to collect and process samples.

7.4.13.2 Hematology

The following hematology tests listed below will be performed:

Table 8. Hematology Panel

red blood cells	white blood cells
Hemoglobin	• total neutrophils
Hematocrit	• eosinophils
mean corpuscular volume (MCV)	• basophils
mean corpuscular hemoglobin (MCH)	• lymphocytes
mean corpuscular hemoglobin concentration (MCHC)	• monocytes
platelet count	

Samples will be analyzed by the central laboratory. Refer to the Central Laboratory Manual for instructions on how to collect and process samples.

7.4.13.3 Serum PK and Bone Turnover Markers - sCTX and P1NP

All blood samples will be obtained by venipuncture before IP administration. The average volume of blood drawn per visit will be approximately 5 mL.

Blood will be obtained at the time points outlined in the Schedule of Assessments (Table 6). The date and time of blood collection will be recorded in the subjects' medical records. Only samples collected from subjects who received romosozumab are planned to be analyzed for romosozumab concentrations.

Serum PK samples will be collected at days 1, 8, 15, 29, 57, 64, 71, 85, 113, and 169/EOS.

Bone turnover marker samples will be collected at days 1, 8, 15, 29, 57, 64, 71, 85, 113, and 169/EOS.

All blood samples will be processed and sent to the central laboratory. The central laboratory will be responsible for completing assays and shipping samples to Amgen for performance of other assays. The central laboratory will be responsible for all serum chemistry, vitamin D, calcium, phosphorous, magnesium, hematology, sCTX, and P1NP, as well as serology assessments. The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all serum samples.

7.4.14 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to romosozumab to investigate the mechanism of action of romosozumab and/or further the biological understanding of OI.

Blood Samples

No additional blood samples will be collected for biomarker development. Potential studies may be pursued using residual samples as noted in Section 7.7.

7.4.15 Hepatitis B, Hepatitis C, and HIV Status

HbsAg, HBcAb, HepCAb, and HIV status will be assessed. If the results show a positive HepCAb: hepatitis C virus RNA by PCR is necessary. The test must be confirmed negative at screening for the subject to be eligible for this study.

Samples will be analyzed by the central laboratory. Refer to the Central Laboratory Manual for instructions on how to collect and process samples.

7.4.16 Concomitant Medications

Concomitant medication(s) will be recorded throughout the study in the source documents and eCRF. Sites will collect therapy name, indication, dose, unit, frequency, route, and start and stop dates for all concomitant medications. Prior medication (medication taken 24 months prior to subject enrolling on study) will also be recorded on the concomitant eCRF.

7.4.17 Adverse Events/Serious Adverse Events

Adverse event and serious adverse event assessments will be made as specified in the Schedule of Assessments (Table 6) and will be evaluated and recorded in the source documents and on the Event eCRF as specified in Section 9. Determination of the

severity of all adverse events will be consistent with the **Severity Intensity** Scale **for Adverse Events** (Appendix A) unless specified otherwise.

7.4.17.1 Adverse Event Data Collection and Adjudication

Any adverse events occurring after the first dose of IP will be recorded in the subjects' medical records and on the appropriate eCRFs. Recording of serious adverse events begins after signing of the informed consent form. Refer to Section 9 for more details. Additional information will be collected for certain adverse events of interest.

The following events will be adjudicated by independent adjudication committees:

Potential Osteonecrosis of the Jaw (ONJ) Events

Cases of ONJ have been reported in association with anti-resorptive 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 pre-specified terms potentially indicative of ONJ, will be reviewed by an independent adjudication committee.

7.5 Antibody Testing Procedures

Blood samples for antibody testing are to be collected (see Schedule of Assessments, Table 6) for the measurement of anti-romosozumab binding antibodies. 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 anti-romosozumab antibodies during the study.

Subjects who test positive for neutralizing antibodies to romosozumab at the final scheduled study visit defined as the end of study visit will be asked to return for additional follow up testing. This testing is to occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of romosozumab. All follow up results, both positive and negative will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-romosozumab antibody

response may also be asked to return for additional follow-up testing. Refer to the Schedule of Assessments (Table 6), as applicable, for specific time points and the laboratory manual for detailed collection and handling instructions.

7.6 Approximate Phlebotomy Volume

Subjects enrolled into this study will agree to provide whole blood for safety, PK, biomarkers and other assessments during their participation in this study as noted in the table below.

Table 9. Approximate Phlebotomy Volume

Test	Approximate Volume per Collection (mL)	# of Collections	Approximate Total Volume (mL)
Chemistry	3	9	27
25 (OH) vitamin D	1	1	1
iPTH	1	8	8
Hematology	2	6	12
HIV, HbsAg, HBcAb, HepCAb	4	1	4
Serum PK	1	10	10
BTM (sCTX and P1NP)	2	10	20
Anti-romosozumab Antibody	2	5	10
Total			92

BTM = bone turnover markers; HbsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HepCAb = hepatitis C antibody; HIV = human immunodeficiency virus; iPTH = intact parathyroid hormone; P1NP = procollagen type 1 N-terminal propeptide; PK = pharmacokinetics; sCTX = serum type I collagen C-telopeptide

7.7 Sample Storage and Destruction

Any blood, biomarker, or PK samples collected according to the Schedule of Assessments (Table 6) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand OI, the dose response and/or prediction of response to romosozumab, 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, biomarker development, 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.

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

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

See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device or other protocol-required therapies and must

discuss with the subject the options for continuation of the Schedule of Assessments (Table 6) 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. Subjects who have discontinued investigational product and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

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

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

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, and/or other protocol required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

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

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

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

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)

- other protocol-specified criteria:
  - pregnancy
  - anaphylactic reaction likely related to IP
  - bone adverse event likely related to IP (eg, atypical femoral fracture)
  - neurologic adverse event likely related to IP (eg, facial cranial nerve-related signs or symptoms)
  - disease flare or medical event requiring treatment not allowed in the protocol
  - severe or symptomatic hypocalcemia
    - Subjects who are removed from treatment as a result of severe or symptomatic hypocalcemia should receive treatment according to local standard of care, at the discretion of the treatment physician and should be closely followed up until resolution of the adverse event.
  - ONJ
  - dental abnormality requiring invasive dental procedures

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject after signing of the ICF through day 169/EOS visit, End of Treatment visit, or 30 days after the last dose of IP (whichever period is longer) are reported using the Events eCRF.

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

procedure while on study, is not considered an adverse event. Change in severity from previously reported grade to another distinct grade (in the opinion of the investigator) should be recorded on the Event eCRF. The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Serious Adverse Events

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

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

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

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

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

9.2 Safety Event Reporting Procedures

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after signing of the ICF through day 169/EOS visit, ET visit, or 30 days after the last dose of IP (whichever period is

longer) are reported using the Events eCRF. The investigator must assign the following adverse event attributes:

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

The adverse event grading scale used will be the **Severity Intensity** Scale **for Adverse Events**. The grading scale used in this study is described in Appendix A.

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

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

The investigator must assess whether the adverse event is possibly related to any study mandated activity (including any screening procedure[s]). This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by a study activity and/or procedure”?

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

clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

If an adverse event severity worsens from the date of onset to the date of resolution, record a single event for each level of severity on the Event eCRF.

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

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through day 169/EOS visit, ET visit, or 30 days after the last dose of IP (whichever period is longer) are reported using the Events eCRF. All serious adverse events must be submitted to Amgen **immediately and no later than** 24 hours following the investigator's knowledge of the event via the Events eCRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via a paper Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event [eSAE] Contingency Report Form) **immediately and no later than** 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet/eSAE Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSAE Contingency Report Form, the data must be entered into the EDC system when the system is again available.

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

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

The investigator must assess whether the adverse event is possibly related to any study mandated activity (including any screening procedure[s]). This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity and/or procedure"?

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

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

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

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

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period (as defined in Section 9.1.2) or after end of study. However, these serious adverse events should be reported to Amgen (regardless of causality) if the investigator becomes aware of them. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen **immediately and no later than** 24 hours following the investigator's knowledge of the event.

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

9.3 Pregnancy and Lactation Reporting

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

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur through day 169/EOS visit, ET visit, or within 3 months after the last dose of Amgen investigational product (whichever period is longer).

The pregnancy should be reported to Amgen Global Patient Safety **immediately and no later than** 24 hours of the investigator's knowledge of the pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

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

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

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

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur through day 169/EOS visit, ET visit or within 3 months after the last dose of investigational product (whichever period is longer).

Any lactation case should be reported to Amgen Global Patient Safety **immediately and no later than** 24 hours of the Investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a pregnancy occurs in a female partner of a male subject, while the subject is in the study, report the pregnancy to Amgen as specified below. In addition to reporting pregnancy during the study (through day 169/EOS or ET), investigators should monitor for pregnancies that occur within 3 months after the last dose with investigational product.

The pregnancy should be reported to Amgen's global Amgen Global Patient Safety **immediately and no later than** 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- Romosozumab serum PK parameters maximum-observed concentration (C_{max}), time to C_{max} (t_{max}), area under the curve (AUC), and terminal half-life ($t_{1/2}$)

10.1.1.2 Secondary Endpoints

- Treatment-emergent adverse events, including events of injection site reactions and changes in cranial nerve function
- Vital signs, electrocardiograms, physical examinations and safety laboratory tests, including serum calcium and phosphorous
- Incidence of antiromosozumab antibodies
- Bone turnover markers including serum P1NP and sCTX measurements
- Lumbar spine BMD, bone mineral content (BMC), bone area, and BMD Z-score as assessed by DXA

10.1.2 Analysis Sets

10.1.2.1 Full Analysis set

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

10.1.2.2 Safety Analysis set

The safety analysis set includes all subjects in the full analysis set who received as least 1 dose of investigational product.

10.1.2.3 PK Analysis set

The PK analysis set will consist of all subjects for whom at least 1 PK parameter or endpoint can be adequately estimated.

10.1.2.4 PD Analysis set

The PD analysis set will consist of all subjects for whom at least 1 PD parameter or endpoint can be adequately estimated.

10.1.2.5 Bone Mineral Density Analysis Set

The BMD analysis set includes subjects in the full analysis set who have a baseline lumbar spine DXA BMD measurement and at least 1 post-baseline lumbar spine DXA BMD measurement.

10.1.3 Covariates and Subgroups

No subgroup analysis is planned.

10.1.4 Handling of Missing and Incomplete Data

The frequency of missing and incomplete data is expected to be low in this study and therefore, missing data will not be imputed.

10.2 Sample Size Considerations

The sample size is based on practical considerations. At least 16 subjects and up to approximately 24 subjects will be enrolled into the study.

10.3 Planned Analyses

10.3.1 Final Analysis

The final analysis will occur after all subjects have completed the study.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, and PD end points. Descriptive statistics on continuous measurements will include means, medians, standard deviations, quartiles and ranges, while categorical data will be summarized using frequency counts and percentages.

10.4.2 Primary Endpoint(s)

Serum romosozumab concentrations will be determined using a validated assay. Individual serum concentration-time plots for romosozumab will be presented for each subject as well as mean concentration-time plots for each dose cohort. PK parameters will be estimated using either compartmental (eg, PK modelling) or non-compartmental methods. Actual dosing and sampling times will be used for calculation of PK parameters. Summary statistics will be generated for each PK parameter for each dose cohort.

10.4.3 Secondary Endpoint(s)

10.4.3.1 Bone Turnover Markers

Actual values and percent changes from baseline in each parameter (P1NP and sCTX) will be descriptively summarized for each dose cohort at each visit.

10.4.3.2 BMD DXA

Actual value and percent change from baseline in BMD at the AP lumbar spine will be descriptively summarized at each visit for each dose cohort. The change from baseline in BMD Z-score at lumbar spine will be checked against weighted estimated mean (SE) of 0.01 (0.09) (95%CI: -017, 0.18) based on meta-analysis result from historical controls

(Letocha et al, 2005; Rauch et al, 2009; Ward et al, 2011). The results from the historical controls will contextualize the observed BMD results at the dose level review meeting.

10.4.3.3 Vital Signs

Vital signs will be reviewed for each subject. Depending on the size and scope of changes, summaries of vital sign data over time and/or changes from baseline over time may be provided.

10.4.3.4 ECG

Electrocardiogram data will be listed and reviewed for each subject. Depending on the size and scope of changes, summaries of ECG data over time and/or changes from baseline over time may be provided.

10.4.3.5 Physical Examinations

Height and weight data will be reviewed for each subject. Individual subject results will be examined in relation to baseline recordings. Depending on the size and scope of changes in data, summaries of physical examinations data over time and/or changes from baseline may be provided.

10.4.3.6 Safety Laboratory Tests

Actual values and changes from baseline in each parameter will be descriptively summarized for each dose cohort at each visit. For serum calcium, phosphorous, and magnesium the percent change from baseline also will be provided.

Shifts in laboratory parameters between baseline and the most extreme post baseline values will be assessed base on the **Severity Intensity** Scale **for Adverse Events**. All laboratory analyses will be based on the safety analysis set.

10.4.3.7 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term according to the medical dictionary for regulatory activities (MedDRA) terminology. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from IP or other protocol-required therapies and adverse events of interest (eg, hypocalcemia, adverse events potentially related to hypersensitivity, malignancy, injection site reactions, hyperostosis, osteoarthritis, and serious cardiovascular events) will also be provided. The number and percentage of subjects reporting adverse events will be evaluated for each dose cohort, across dose cohorts, and will also be tabulated by relationship to study drug. Adverse events resulting in treatment discontinuation will be identified.

10.4.3.8 Anti-romosuzomab Antibodies

Immunogenic response during the study will be described by tabulating the numbers and percentages of subjects who tested positive for (binding and neutralizing) anti-romosuzomab antibodies based on the safety analysis set.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

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

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

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

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

with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative.

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

Assent from the child and consent from the parents or legally acceptable representatives must be obtained. 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. For specific local information, consult the country specific requirements of the applicable countries.

11.2 Institutional Review Board/Independent Ethics Committee

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

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

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

11.3 Subject Confidentiality

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

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.

- On the demographics page, in addition to the unique subject identification number, include the age at the 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 date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in strict confidence by the investigator, except as described below.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named such individuals to have access to his/her study related records, including personal information.

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in

writing of the study's completion or early termination and send a copy of the notification to Amgen.

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

12.2 Study Documentation and Archive

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

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

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 eCRF, informed consent 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 (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.

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

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

12.3 Study Monitoring and Data Collection

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

The Clinical Monitor is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study related records needed to verify the entries on the eCRFs.

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

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

Data capture for this study is planned to be electronic:

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

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 6), the investigator can search publicly available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

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

Electronic CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

12.6 Publication Policy

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

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

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

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

12.7 Compensation

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

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

13. REFERENCES

Bachrach LK. Osteoporosis in children: still a diagnostic challenge. *J Clin Endocrinol Metab.* 2007;92:2030-2032.

Balemans W, Ebeling M, Patel N, et al. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). *Hum Mol Genet.* 2001;10:537-543.

Beighton P, Durr L, Hamersma H. The Clinical features of Sclerostosis. A review of the manifestations in twenty-five affected individuals. *Annals of Intern Med*. 1976;84; 393-397.

Bishop N, Adami S, Ahmed SF, et al. Risedronate in children with osteogenesis imperfecta: a randomized double-blind, placebo-controlled trial. *Lancet.* 2013;382:1424-1432.

Brunkow ME, Gardner JC, Van Ness J, et al. Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. *Am J Hum Genet.* 2001;68:577-589.

Byers PH. Osteogenesis imperfecta: Perspectives and opportunities. *Curr Opin Pediatr.* 2000;12:603-609.

Castillo H, Samson-Fang L, American Academy for Cerebral P, Developmental Medicine Treatment Outcomes Committee Review P. Effects of bisphosphonates in children with osteogenesis imperfecta: an AACPDM systematic review. *Dev Med Child Neurol.* 2009;51:17-29.

Cheung MS and Glorieux FH. Osteogenesis imperfecta: Update on presentation and management. *Rev Endocr Metab Disord*. 2008; 9(2):153–160.

Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;375:1532-1543.

Dawson-Hughes B, Dallal GE, Krali EA et al. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med.* 1990; 323:878-83

Dawson-Hughes B, Mithal A, Bonjour J-P, et al. IOF position statement: vitamin D recommendations for older adults. *Osteoporosis Int.* 2010; 21: 1151-1154.

EU Ethical Considerations. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. 2016. https://ec.europa.eu/health//sites/health/files/files/clinicaltrials/2016_06_pc_guidelines/gl_1_consult.pdf

EVENITY® prescribing information, Thousand Oaks, CA: Amgen Inc.

Fasanmade AA, Adedokun OJ, Blank M, Zhou H, Davis HM. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. *Clin Ther*. 2011;33:946-964.

Glade Bender JL, Adamson PC, Reid JM, et al. Phase I trial and pharmacokinetic study of bevacizumab in pediatric patients with refractory solid tumors. *J Clin Oncol*. 2008;26:399-405.

Gordon MS, Margolin K, Talpaz M, et al. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. *J Clin Oncol.* 2001;19:843-850.

Graeff C, Campbell GM, Peña J, et al. Administration of romosozumab improves vertebral trabecular and cortical bone as assessed with quantitative computed tomography and finite element analysis. *Bone*. 2015;81:364-369.

Hamersma H, Gardner J, Beighton P. The natural history of sclerosteosis. *Clin Genet.* 2003;63:192-197.

Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Dietary Reference Intakes for Calcium and Vitamin D. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Washington (DC): National Academies Press (US); 2011. PMID: 21796828.

Langdahl BL, Libanati C, Crittenden DB, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. *Lancet.* 2017;390:1585-1594.

Li X, Ominsky MS, Warmington KS, et al. Sclerostin antibody treatment increases bone formation, bone mass, and bone strength in a rat model of postmenopausal osteoporosis. *J Bone Miner Res*. 2009;24:578-588.

Li X, Warmington KS, Niu Q, et al. Bone formation without increasing bone resorption in aged male rats. *J Bone and Mineral Res*. 2007a;22(Suppl. 1):S36.

Li X, Warmington KS, Niu QT, et al. Treatment with an anti-sclerostin antibody directly stimulates bone formation in a dose-dependent manner in ovariectomized rats with established osteopenia. *J Bone Miner Res*. 2007b;22(Suppl. 1):S65.

Ludvigsson JF Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatrica. 2020;10

Mäkitie, O. Causes, Mechanisms and management of paediatric osteoporosis. *Nat. Rev. Rheumatol.* 2013;9:465–475.

Marini JC, Blissett AR. New Genes in Bone Development: What's new in osteogenesis imperfecta. *J Clin Endocrinol Metab.* 2013;98:3095-3103.

McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med*. 2014;370(5):412-20.

Ominsky M, Samadfam R, Jolette J, et al. Long-term sclerostin antibody treatment in cynomolgus monkeys: Sustained improvements in vertebral microarchitecture and bone strength following a temporal increase in cancellous bone formation. *J Bone Miner Res*. 2012;27 (Suppl 1): Abstract 0406. Available at http://www.asbmr.org/Meetings/AnnualMeeting/AbstractDetail.aspx?aid=5f87a06d-4d04-4654-b657-18f42c0f900f (accessed 09 Nov 2017).

Ominsky MS, Boyce RW, Li X, Ke HZ. Effects of sclerostin antibodies in animal models of osteoporosis. *Bone* 2017;96:63-75.

Ominsky MS, Li CY, Li X, et al. Inhibition of sclerostin by monoclonal antibody enhances bone healing and improves bone density and strength of non-fractured bones. J Bone Miner Res. 2011 May;26:1012-21.

Ominsky MS, Niu QT, Kurimoto P, Ke HZ. Tissue level mechanism of increased bone formation by sclerostin antibody in male cynomolgus monkeys. *J Bone Miner Res.* 2010:25(Suppl. 1):S53.

Orwoll ES, Shapiro J, Veith S, et all. Evaluation of teriparatide treatment in adults with osteogenesis imperfecta. *J Clin Invest*. 2014;124:491-498.

Padhi D, Allison M, Kivitz AJ, et al. Multiple doses of sclerostin antibody romosozumab in healthy men and postmenopausal women with low bone mass: a randomized, double-blind, placebo-controlled study. *J of Clin Pharmacol*. 2014;54:168-178.

Padhi D, Jang G, Stouch B, Fang L, Posvar E. Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. *J Bone Miner Res.* 2011;26:19-26.

Poole KE, van Bezooijen RL, Loveridge N, et al. Sclerostin is a delayed secreted product of osteocytes that inhibits bone formation. *Faseb J.* 2005;19:1842-1844.

Rauch F, Glorieux FH. Osteogenesis imperfecta. *Lancet.* 2004;363:1377-1385.

Rauch F, Munns CF, Land C, Cheung M, Glorieux FH. Risedronate in the treatment of mild pediatric osteogenesis imperfecta: A randomized placebo-controlled study. *J Bone Miner Res*. 2009;24:1282-1289.

Romosozumab Investigator's Brochure. Thousand Oaks, CA: Amgen Inc.

Ross AC, Manson JE, Abrams SA et al. The 2011 Report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. *J Clin Endocrinol Metab.* 2011; 96: 53-59.

Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med*. 2017;377:1417-1427.

Shah AD, Shoback D, Lewiecki ME. Sclerostin inhibition: A Novel Therapeutic Approach in the Treatment of Osteoporosis. *Int J Women's Health*. 2015; 7: 565-580.

Steiner RD, Adsit J, Basel D. COL1A1/2-Related Osteogenesis Imperfecta. In: Pagon RA, Adam M.P., Bird T.D., et al., ed. GeneReviews: University of Washington, Seattle; 2005

Synopsis *20060220 & 20060221*

Trippett TM, Herzog C, Whitlock JA, et al. Phase I and Clinical Pharmacology: Phase I and Pharmacokinetic Study of Cetuximab and Irinotecan in Children with Refractory Solid Tumors: A Study of the Pediatric Oncology Experimental Therapeutic Investigators' Consortium. *J Clin Oncol*. 2009;5102-5108.

Turkalj M, Miranovic V, Lulic-Jurjevic R, Juraski RG, and Promorac D. Cardiorespiratory complications in patients with osteogenesis imperfecta. Paediatr Croat. 2017; 61:106-12.

Van Bezooijen RL, Roelen BAJ, Visser A, et al. Sclerostin is an Osteocyte-expressed Negative Regulator of Bone Formation, But Not a Classical BMP Antagonist. *J Exp Med.* 2004;199:805-814.

van Dijk FS, Byers PH, Dalgleish R, et al. EMQN Best Practice Guidelines for the Laboratory Diagnosis of Osteogenesis Imperfecta. *Eur J Hum Genet.* 2012;20:11-19.

Vanhoenacker FM, Balemans W, Tan GJ, et al. Van Buchem disease: Lifetime evolution of radioclinical features. *Skeletal Radiol.* 2003;32:708-718.

Vuorimies I, Mäyränpää MK, Valta H et al. Bisphosphonate Treatment and the Characteristics of Femoral Fractures in Children With Osteogenesis Imperfecta. *J Clin Endocrinol Metab.* 2017; 102(4): 1333–1339, 2017

Ward LM, Konji VN, Ma J. The Management of Osteoporosis in Children. *Osteoporos Int.* 2016;27(7):2147-79.

Ward LM, Rauch F, Whyte MP et al. Alendronate for the treatment of pediatric osteogenesis imperfecta: a randomized placebo-controlled study. *J Clin Endocrinol Metab*. 2011; 96(2):355-364.

Winkler DG, Sutherland MK, Geoghegan JC, et al. Osteocyte Control of Bone Formation via Sclerostin, a novel BMP Antagonist. *EMBO J.* 2003;22:6267-6276.

14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

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 Severity Intensity Scale for Adverse Events as shown below:

Grade	Definition
MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity
SEVERE	Incapacitating with inability to work or do usual activity

[a] An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

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

- The event is to be reported to Amgen as a serious adverse event **immediately and no later than** 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate eCRF (eg, Adverse Event eCRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product (IP) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.4.1 and Section 6.4.2 or who experience AST or ALT elevations > 3 x ULN or 2-fold increase above baseline values for subjects with evaluated 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, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBIL > 2x 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(s) 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 total bilirubin. The following are to be considered depending on the clinical situation:
  - Complete blood count (CBC) with differential to assess for eosinophilia
  - Serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) 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
  - CPK, haptoglobin, LDH, 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 an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, total bilirubin, 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 all investigational product(s) and protocol-required therapies.

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

Appendix B. Electronic Serious Event Contingency Form

A Study # 20160227 AMG 785	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

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

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

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

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

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? AMG 785 No✓ Yes✓ *Placebo* No✓ Yes✓ *Placebo* No✓ Yes✓ *Placebo* 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; **02** Immediately life-threatening; **03** Required/prolonged hospitalization; **04** Persistent or significant disability /incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

IP/Amgen Device:		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 #
AMG 785	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____

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A Study # 20160227 AMG 785	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

								☐ Unavailable / Unknown

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

A Study # 20160227 AMG 785	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

Appendix C. Pregnancy and Lactation Notification Worksheets

Amgen 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: 20160227

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

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: 20160227

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

Superseding Amendment 3

Protocol Title: An Open-label, Ascending Multiple-dose Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Romosozumab in Children and Adolescents With Osteogenesis Imperfecta

Amgen Protocol Number: Romosozumab 20160227

EudraCT number: 2017-004972-74

NCT Number: 04545554

Amendment Date: 28 February 2023

Rationale:

The protocol is being amended to correct that most laboratory assessments are to be completed by the Central Laboratory as the Schedule of Assessments erroneously listed them to be completed by the Local Laboratory. Safety language was also updated throughout to align with current template.

Amendment 3

Protocol Title: An Open-label, Ascending Multiple-dose Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Romosozumab in Children and Adolescents With Osteogenesis Imperfecta

Amgen Protocol Number (AMG 785) 20160227

EudraCT Number 2017-004972-74

Amendment Date: 19 February 2021

Rationale:

The rationale for this protocol amendment is to include following:

- To update the schedule of assessments table and throughout the protocol to include following visits 2 hours post dose (day 1), day 43, and remove day 61 visit
- To update the schedule of assessments table footnotes to detail information about the home care services and assessments can be performed at home
- To update the study design to include the subject monitoring details for 2 hours after the first and subsequent dosing of romosozumab
- To update the schedule of assessment table with alcohol and drug testing and echocardiogram, telephonic safety assessments at screening visits
- To update the pediatric risk assessment language to include risk of valvular heart disease and safety monitoring to include neurological assessments
- To update the pediatric risk assessment to include the language for subject monitoring for at least 2 hours following the first and subsequent dosing of romosozumab.
- To include details of potential COVID-19 risks in the pediatric risk assessment
- To update the study rationale to include details of romosozumab pharmacokinetic model for children
- To update the Subject Enrollment with the subject screening language to provide additional details of subjects' enrollment and subject identification number
- To add the exclusion criteria # 235 to include clinically significant valvular heart disease
- To include drug substances of abuse along with alcohol and tobacco restrictions
- To update the Contraceptive Requirements with the contraception language to include progesterone-only hormonal contraception language and remove two-barrier methods
- To update the language to include reporting of adverse events after signing the informed consent form through the end of study
- To remove the language for the worldwide reporting regulations for all adverse events unblindingfrom Reporting Procedures for Serious Adverse Events
- To include Bone Mineral Density Analysis Set

- Remove ‘by treatment group’ for the statistical considerations
- To update the subject enrollment identification number to include incremental order within each site starting at 301
- To correct the formatting, editorial, abbreviation, and grammatical spelling errors throughout the document

Amendment #2

Protocol Title: An Open-label, Ascending Multiple-dose Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Romosozumab in Children and Adolescents With Osteogenesis Imperfecta

Amgen Protocol Number AMG 785 20160227

Amendment Date: 26 May 2020

Rationale:

The protocol is being amended to make the following changes:

- Assess COVID 19 risk in relation to study population and mechanism of action of romosozumab
- Updated rational for dose selection
- Updated subject screening number assignment from manual process to using interactive response technology (IRT).
- Administrative corrections.

Amendment #1

Protocol Title: An Open-label, Ascending Multiple-dose Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Romosozumab in Children and Adolescents With Osteogenesis Imperfecta

Amgen Protocol Number AMG 785 20160227

Amendment Date: 27 April 2020

Rationale:

The protocol is being amended to make the following changes:

- The placebo group was removed from the study as this is mainly a dose-finding study and data from the placebo group were not deemed necessary to compare the pharmacokinetics and pharmacodynamics from the different doses of romosozumab. Increase number of subjects with active treatment from 3 to 4 will also contribute to better understanding of PK variability at each dose level. Updates to the protocol language and procedures were made to align with the new open-label non-randomized study design. Each cohort size remains at n = 4
- Hip dual energy x-ray absorptiometry (DXA) was removed. This site can be very challenging to image in a pediatric population and the expectation that BMD will change in a 3-month setting is low, therefore this imaging site was removed.
- Bone mineral density (BMD), bone mineral content and bone area were added as DXA parameters in the secondary endpoints. These data are routinely reported with BMD Z-scores and will help to interpret results
- The dose level review meetings were renumbered, and language was updated to clarify the activity
- The background section was updated to include information on the approved indication for romosozumab
- The risk section was reorganized into a single “Pediatric Risk Assessment” rather than one section discussing a general risk assessment and another section discussing risks only relevant to the pediatric population. The section was streamlined, and the reader is referred to the romosozumab Investigational Brochure for additional safety information.
- Addition of ECG assessment on day 29
- Addition of serum PK collection to end of study (day 169) and removing day 61 PK sample to be consistent with ADA collection. Added ADA collection to day 15

- Pregnancy testing at screening will be done using serum samples, but all other pregnancy assessments will remain unchanged using urine samples
- Addition of exclusion criterion 205 to exclude subjects with body weight less than 10 kg and greater than 90 kg
- Additional conditions associated with increased risk of cardiovascular disease were added to exclusion criterion 207 to minimize risk to subjects
- Exclusion criterion 209 was updated to clarify that removal of baby teeth is not considered an invasive dental procedure
- Modification of exclusion criterion 221 to only exclude subjects within 12 months of prior denosumab use
- Common Terminology Criteria for Adverse Events grading scale was replaced with The Amgen Standard Grading Scale as it was deemed more appropriate for the study design and population
- Language in Table 3. Cohort Dose Stopping Rules was updated to reflect the sponsor's current guidance for cohort dose stopping rules and to remove reference to unblinding since the study is now open-label
- Tanner staging was removed. A history of menarche will solely be used to determine whether female subjects will undergo pregnancy testing.
- Adjudication of atypical femoral fractures was removed for the following reason: recent publications report that a femoral fracture is one of the most common fracture sites in children with osteogenesis imperfecta (Folkestad et al, 2017) with radiographic appearances that cannot be distinguished from atypical femoral fractures (AFF) in adults with primary osteoporosis (Nicolaou et al, Trejo et al, Vuorimies et al).
- Adjudication of potential cardiovascular events was removed. It is unexpected that a cardiovascular event will occur in this study, but if one should occur it will be thoroughly investigated. A specific adjudication process was not deemed necessary.
- Disease-related events were removed from the protocol to align with Amgen's current processes for reporting adverse events. The anticipated serious adverse event definition was removed from the protocol because all serious adverse events will be reported to health authorities in an expedited manner.
- Clarification on analysis plan for BMD DXA
- Language in the protocol describing Self-Evident Corrections was removed from the protocol to align with Amgen's current processes
- Other changes to improve readability, correct grammar and/or remove duplicated information were made throughout the protocol.

References:

Folkestad L, Hald JD, Ersboll AK, et al. Fracture rates and fracture sites in patients with osteogenesis Imperfecta: a nationwide register-based cohort study. *J Bone Miner Res*. 2017;32:125–134.

Nicolaou N, Agrawal Y, Padman M, Fernandes JA, Bell MJ. Changing pattern of femoral fractures in osteogenesis imperfecta with prolonged use of bisphosphonates. *J Child Orthop*. 2012;6:21-27.

Trejo P, Fassier F, Glorieux FH, Rauch F. Diaphyseal femur fractures in osteogenesis imperfecta: characteristics and relationship with bisphosphonate treatment. *J Bone Miner Res*. 2017;32:1034-1039.

Vuorimies I, Mäyränpää MK, Valta H, Kröger H, Toiviainen-Salo S, Mäkitie O. Bisphosphonate treatment and the characteristics of femoral fractures in children with osteogenesis imperfecta. *J Clin Endocrinol Metab*. 2017;173:806-808.