Title Page

Protocol Title:		An Open-label, Single-arm, Multicenter Phase 4 Study to Evaluate Safety and Tolerability of Romosozumab (EVENITY®) in Postmenopausal Women in India with Osteoporosis and a High Risk of Fracture
Short Protocol Title:		A Study of Romosozumab (EVENITY®) in Postmenopausal Women in India with Osteoporosis at a High Risk of Fracture
Protocol Number:		20210025
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Trade Name:		EVENITY®
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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (International Council for Harmonization [ICH] E6).

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Investigator's Agreement:

I have read the attached protocol entitled An Open-label, Single-arm, Multicenter Phase 4 Study to Evaluate Safety and Tolerability of Romosozumab (EVENITY®) in Postmenopausal Women in India with Osteoporosis and a High Risk of Fracture, dated 19 September 2022, and agree to abide by all provisions set forth therein.

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_____
Signature

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Name of Investigator Date (DD Month YYYY)

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Title and Role of Investigator

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Institution Name

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Address and Telephone Number of Institution

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1. Protocol Summary

1.1 Synopsis

Protocol Title: An Open-label, Single-arm, Multicenter Phase 4 Study to Evaluate Safety and Tolerability of Romosozumab (EVENITY®) in Postmenopausal Women in India with Osteoporosis and a High Risk of Fracture

Short Protocol Title: A Study of Romosozumab (EVENITY®) in Postmenopausal Women in India with Osteoporosis at a High Risk of Fracture

Study Phase: Phase 4

Indication: Postmenopausal osteoporosis

Study Rationale

Romosozumab is a humanized monoclonal antibody that inhibits sclerostin and was approved in India on 04 May 2021 for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or subjects who have failed or are intolerant to other available osteoporosis therapy.

This multicenter open-label, single-arm, phase 4 study is designed to fulfil the post-marketing requirement to assess romosozumab in Indian subjects with postmenopausal osteoporosis as per the locally approved label.

Objective(s) and Endpoint(s)/Estimand(s)

Objectives	Endpoints
Primary	
• To characterize safety and tolerability of romosozumab in Postmenopausal women with osteoporosis and a high risk of fracture in India.	• Subject incidence of treatment-emergent adverse events within 12 months. • Subject incidence of treatment-emergent serious adverse events within 12 months. • Change from baseline in laboratory assessments and vital signs at month 12.
Secondary	
• To characterize the efficacy of romosozumab on lumbar spine, total hip, and/or femoral neck BMD in Postmenopausal women	• Percent change from baseline in BMD (measured by DXA) of the lumbar spine at 6 and 12 months.

with osteoporosis and a high risk of fracture in India.	• Percent change from baseline in BMD (measured by DXA) of the total hip at 6 and 12 months. • Percent change from baseline in BMD (measured by DXA) of the femoral neck at 6 and 12 months.
Exploratory	
CCI [redacted]	

BMD = bone mineral density; and DXA = dual-energy x-ray absorptiometry

Overall Design

This multicenter, open-label, single-arm, phase 4 study of romosozumab is part of Amgen's post-marketing requirement to the Central Drugs Standard Control Organization (India Regulatory Authority). The study population consists of approximately 100 Postmenopausal Women subjects in India with Osteoporosis and a High Risk of Fracture for whom romosozumab is indicated in accordance with the approved prescribing information in India. If subject signs the informed consent, then meets the eligibility criteria to receive romosozumab per label and successfully passes the screening process (up to 35 days from the date of informed consent), they will be enrolled at the baseline visit (day 1) and given the first dose of romosozumab. The enrollment period shall stop once 100 enrolled subjects have received their first dose of romosozumab. Each subject will be followed from the first dose of romosozumab until the end of the 12-month period, death, withdrawal of consent, early discontinuation for any reason, or loss to follow-up (eg, subject transferring to another clinic), whichever occurs first. Treatment-emergent adverse events, and treatment-emergent serious adverse events will be collected during the treatment/observation period, and reported for any subject who has received at least 1 dose of romosozumab. Subject incidence of treatment-emergent adverse events and treatment-emergent serious adverse events will be reported and summarized. Treatment efficacy will be determined by percent change from baseline in dual-energy x-ray absorptiometry (DXA) bone mineral density (BMD) of the lumbar spine, total hip, and femoral neck taken at 6 months, and 12 months for any subject who has a baseline DXA BMD measurement and at least 1 post-baseline DXA BMD measurement at the lumbar spine, and received at least 1 dose of romosozumab. All data collected for the purpose of this study will be entered into the electronic case report form (eCRF).

Number of Subjects

Approximately 100 subjects will be enrolled in this single-arm study.

Summary of Subject Eligibility Criteria

Key inclusion criteria include subjects diagnosed with osteoporosis who are postmenopausal and have a high risk of fracture who provide informed consent (in-person or through their legally authorized representative) to participate in the use of romosozumab per the local label in India.

Key exclusion criteria include subjects who experienced myocardial infarction or stroke within a year prior to entering this study.

For a full list of eligibility criteria, please refer to Section 5.1 to Section 5.2.

Treatments

Amgen will provide to sites romosozumab for subcutaneous (SC) administration of 12 monthly 210 mg doses. Romosozumab will be administered in a prefilled syringe (PFS) SC injection of a fixed dose of 105 mg in a 1.17 mL deliverable volume. A full (monthly) dose of 210 mg comprises of 2 PFS injections. All SC injections must be administered by authorized site healthcare personnel.

To minimize the risk of hypocalcemia during romosozumab treatment, subjects should be adequately supplemented with calcium (500 to 1,000 mg) and vitamin D (600 to 800 IU) from screening to end of study participation. Calcium and vitamin D will not be provided by Amgen (except if required by local regulation) and will be provided by investigators per local standard of care.

Statistical Considerations

Subject incidence of treatment-emergent adverse events, treatment-emergent serious adverse events, fatal adverse events, and adverse events leading to discontinuation from investigational product will be provided. Changes from baseline in vital signs and laboratory assessments (serum chemistry and hematology) at month 12 will also be summarized.

With 100 subjects, there is a 95% chance of observing ≥ 1 adverse event, if the actual event rate is 3% or more.

Also, this study has a 99% power to detect a mean BMD percentage change from baseline of 10% or more in the lumbar spine at month 12 assuming the percent change

from baseline of lumbar spine BMD at month 12 has mean 13.1% and standard deviation 5.5%.

For a full description of statistical analysis methods, please refer to Section 9.

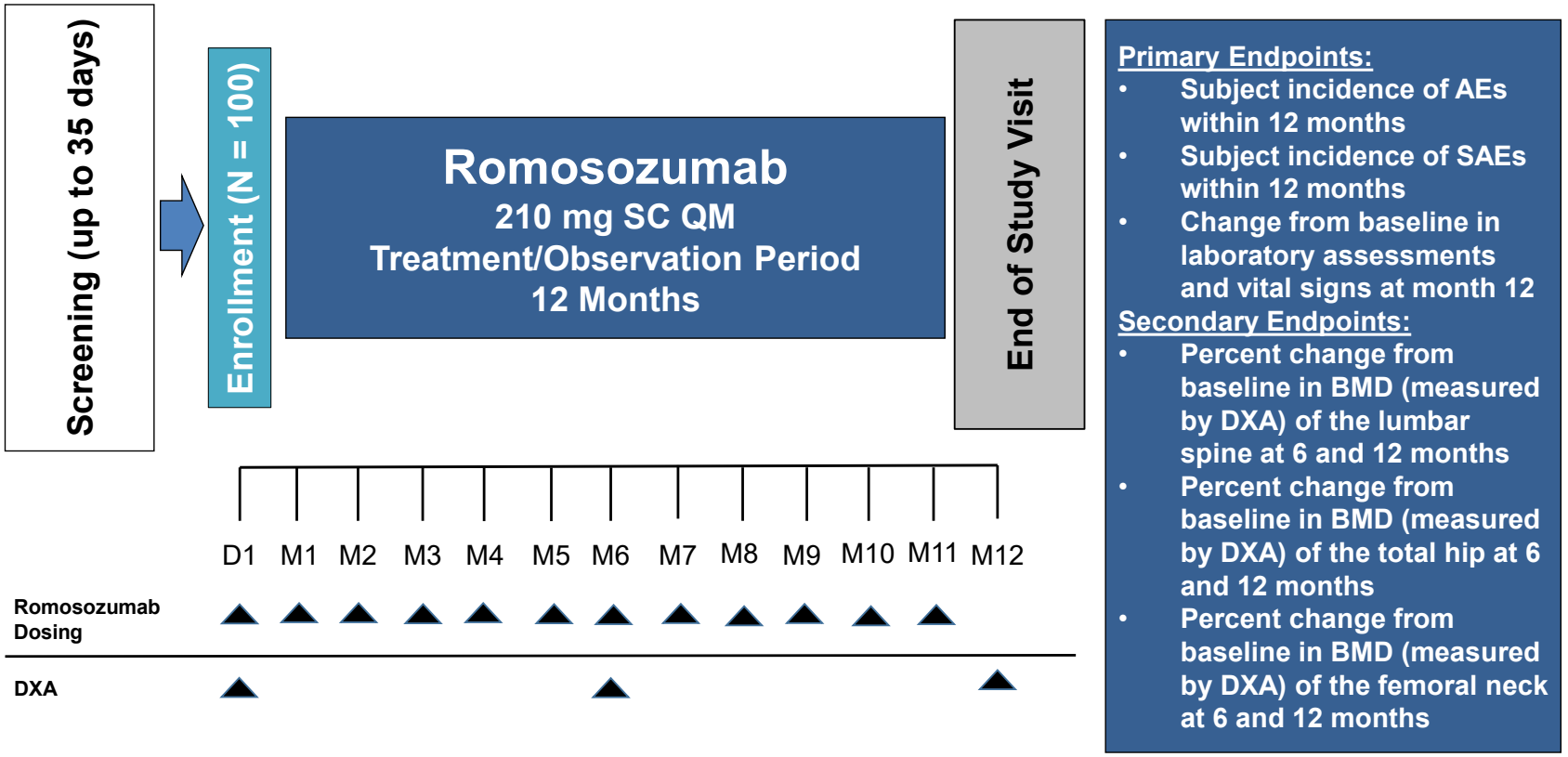
Statistical Hypotheses

There is no statistical hypothesis for primary endpoint.

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



AE = adverse event; BMD = bone mineral density; QM = once monthly; SAE = serious adverse events; SC = subcutaneous; DXA = dual-energy x-ray absorptiometry; M = month; D = day

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities

Procedure	Screening (Up to 35 Days Before Day 1)	Treatment Period[a]												End of Study	
		Enrollment Visit/Day 1	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	Early Termination Visit[m]	M12
GENERAL AND SAFETY ASSESSMENTS															
Informed consent	X														
Eligibility	X														
Demographics	X														
Height	X														
Weight	X														
Physical exam	X													X	X
Medical history	X														
Targeted medical history[b]	X														
Vital signs	X	X						X						X	X
Electrocardiogram	X														
Adverse events[c]		←													→
Serious adverse events[c,d]	←														→
Concomitant therapies review[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Instructions for daily vitamin D and calcium supplementation	X	X						X						X	X
Serum chemistry/hematology[f]	X	X	X		X			X			X			X	X

Footnotes defined on final page of this table.

Table 1-1. Schedule of Activities

Procedure	Screening (Up to 35 Days Before Day 1)	Treatment Period[a]												End of Study	
		Enrollment Visit/Day 1	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	Early Termination Visit[m]	M12
GENERAL AND SAFETY ASSESSMENTS															
Serum 25 (OH) vitamin D	X														
Romosozumab concentration[g]		X	X		X			X			X			X	X
If applicable: vitamin D loading dose (at least 50,000 to 60,000 IU, preferably by the oral route)		X													
IMAGING ASSESSMENTS															
Lateral Spine x-rays (lumbar and thoracic)	X														
DXA (lumbar spine, total hip, and femoral neck)		X[h]						X[i]						X[j]	X[k]
STUDY TREATMENT															
Romosozumab injection at investigation site by healthcare professional[l]		X[n]	X	X	X	X	X	X	X	X	X	X	X		

DXA = dual-energy x-ray absorptiometry; M = month

[a] The target date for each monthly study visit (post day 1) should be calculated based on consecutive 30-day intervals from the date of the first romosozumab dose on day 1. All monthly study visits up to the month 12 study visit should have a ± 7-day window.

[b] Targeted medical history (collected only during screening) includes the following:

- date of diagnosis of postmenopausal osteoporosis
- history of metabolic bone disease
- cardiovascular disease
- chronic kidney disease
- hepatic impairment (Child-Pugh class A, B, or C)

- hypocalcemia (including any other underlying medical history that may predispose to low serum blood calcium)
- hypersensitivities (including drug allergies, environmental allergies, angioedema, anaphylaxis history, rash, dermatitis, and urticaria)
- osteonecrosis of the jaw (including tooth extractions and location of extraction, denture use, and jaw pain left or right side)
- atypical femoral fracture (including past hip fractures [specify location], and hip pain [specify location, ie, lateral side of hip and left or right side])
- smoking status (past and present)

[c] Include adverse events, serious adverse events, other safety findings, and spontaneously reported product complaints. Safety events reported by subjects spontaneously from the time of first dose until up to 30 days after administration of final dose of romosozumab will be collected.

[d] Once the study has ended, serious adverse events will be reported to Amgen (regardless of causality) if the investigator becomes aware of a serious adverse event. Please refer to Section 8.4.5.1.2 for additional details.

[e] For concomitant therapies being taken for osteoporosis, record all history. For all other concomitant therapies, record history from 5 years before starting the study through the signing of the informed consent form.

[f] Please refer to Table 11-1 (Analyte listing) for central laboratory tests to be performed.

[g] CCI .

[h] For baseline DXAs (lumbar spine, total hip, and femoral neck): DXA scans can be obtained during the screening period (up to 35 days) prior to day 1 to facilitate subject scheduling for the day 1 visit, or at the day 1 visit.

[i] For month 6 DXAs (for lumbar spine, total hip, and femoral neck): The month 6 DXA can be taken at the target date for the month 6 visit (calculated on a consecutive 30-day intervals from the date of the day 1 visit) ± 2 weeks.

[j] For Early Termination Visit DXAs (for lumbar spine, total hip, and femoral neck): The Early Termination DXA can only be taken if Early Termination Visit falls within the month 6 visit target date (calculated on a consecutive 30-day intervals from the date of day 1) (±2 weeks).

[k] For month 12 DXAs (for lumbar spine, total hip, and femoral neck): The month 12 DXA can be taken at the month 12 visit target date (calculated on a consecutive 30-day intervals from the date of the day 1 visit) ±2 weeks.

[l] Romosozumab administration must be the last procedure at each applicable visit. A full dose of romosozumab is administered with two single-use prefilled syringes. The second single-use prefilled syringe must be administered immediately after the first syringe injection is completed. All efforts should be made to administer romosozumab within the defined study visit windows. In case of an out-of-window visit, romosozumab can be administered ± 2 weeks of the target visit date (calculated on a consecutive 30-day intervals from the date of the day 1 visit). If romosozumab cannot be administered ± 2 weeks of the target visit date, the dose must be considered missed.

[m] Subjects who terminate participation in the study early, should complete the end of study assessments approximately 30 (± 3) days after the end of the last dose of romosozumab (refer to Section 8.1.3).

[n] If it is not possible to administer the first dose at the enrollment visit, it must be administered within 72 hours of the enrollment visit date. Day 1 is defined as the date of the first dose.

2. Introduction

2.1 Study Rationale

Romosozumab is a humanized monoclonal antibody that inhibits sclerostin and was approved in India on 04 May 2021 for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or subjects who have failed or are intolerant to other available osteoporosis therapy.

This multicenter open-label, single-arm, phase 4 study is designed to fulfil the post-marketing requirement to assess romosozumab in Indian subjects with postmenopausal osteoporosis as per the locally approved label.

2.2 Background

2.2.1 Disease

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture (National Institutes of Health [NIH] Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001). It is estimated that approximately 46 million women in India above the age of 50 suffer from osteoporosis (Khadilkar and Mandlik, 2015, Mithal et al, 2014). Despite availability of several therapies, treatment remains suboptimal; even effective anabolic agents like teriparatide have limited applicability possibly because of the inconvenience of daily injections.

2.2.2 Amgen Investigational Product Background: Romosozumab (EVENITY®)

Romosozumab is an immunoglobulin G2 humanized monoclonal antibody that binds and inhibits sclerostin, thereby increasing Wingless-related integration site (Wnt) signaling in bone (Padhi et al, 2011; Paszty et al, 2010). Romosozumab has a dual effect on bone, increasing bone formation and decreasing bone resorption (McClung et al, 2014; Ominsky et al, 2014).

Study 20070337 was a phase 3, multicenter, international, randomized, double-blind, placebo-controlled, parallel-group study in postmenopausal women with osteoporosis. This study was designed to evaluate if romosozumab treatment for 12 months compared with placebo was effective in reducing the incidence of new vertebral fractures, and if romosozumab treatment for 12 months followed by denosumab treatment for 12 months was effective in reducing the incidence of new vertebral fractures compared with

12 months of placebo followed by denosumab treatment for 12 months in postmenopausal women with osteoporosis.

In Study 20070337, the romosozumab global efficacy results showed a significantly reduced risk of new vertebral fractures in postmenopausal women with osteoporosis through month 12 compared with placebo, with a reduction in fracture risk becoming apparent by month 6. The risk reduction at month 12 persisted through month 24 after both treatment groups transitioned to antiresorptive therapy (denosumab). The global efficacy results also demonstrated that romosozumab treatment led to rapid and significant increases in BMD at the lumbar spine, total hip, and femoral neck. Clinically significant increases in BMD were seen in the first 6 months, and the increases continued through 12 months, and were maintained following transition to antiresorptive therapy (denosumab) after the 12-month romosozumab treatment period.

Of the 7180 subjects enrolled in Study 20070337, 106 were Indian. Results from the subset of Indian subjects indicated that:

- Efficacy results in the Indian subjects were similar to those of the global population. Among the Indian subjects, romosozumab significantly increased BMD at the lumbar spine, total hip, and femoral neck compared with placebo at month 12. Romosozumab followed by denosumab resulted in continued increases in BMD at the lumbar spine, total hip, and femoral neck at month 24.
- During the 12-month double-blind period, the overall subject incidence of adverse events and serious adverse events were similar between the Indian subjects and the global population. No adverse events leading to discontinuation of investigational product or study were reported for the Indian subjects.

Among the Indian subjects, during the double-blind period, 4 positively adjudicated CV serious adverse events were reported for 3 subjects (6.1%) in the romosozumab group and no subject in the placebo group. Of these, 3 positively adjudicated CV serious adverse events were counted among cardiovascular deaths, and included a 70-year-old female subject with history of long standing hypertension and diabetes mellitus who developed cardiorespiratory arrest while recovering from diabetic ketoacidosis; a 71-year-old female subject with history of long standing hypertension and diabetes mellitus who was receiving concomitant medications for arrythmia and heart failure before developing a fatal event of congestive cardiac failure; and a 76-year-old female subject with pre-existing long standing hypertension who had a cardiac arrest. None of

these deaths was considered to be related to investigational product by the investigator. Based on review of the individual cases and taking into consideration the small number, the cardiovascular safety profile in Indian subjects is considered consistent with the global population.

A review of the mean lumbar spine BMD percent change from baseline at 12 months of several comparators to romosozumab (bone-forming agents and antiresorptive therapies) was done to determine a cut-off mean percent change that would demonstrate a greater treatment effect of romosozumab over its comparators after 12 months of treatment. For this phase 4 study in India, it has a 99% power to detect a mean BMD percentage change from baseline of 10% or more in the lumbar spine, which signifies a greater treatment effect than other approved therapy for postmenopausal osteoporosis with a high risk of fracture in postmenopausal women.

2.3 Benefit/Risk Assessment

Postmenopausal osteoporosis is a chronic progressive disease that increases the risk of fractures. After an osteoporosis-related fracture, the risk of a subsequent fracture is 5-fold higher in the first year and remains elevated for 10 years. Even if recovery after the first fracture allows a woman to remain pain-free and independent, subsequent fractures will ultimately lead to chronic pain, loss of independence and earlier death, compared to postmenopausal women who have not suffered fractures. There is a clear unmet need in women with osteoporosis at high risk for fracture, particularly those with a recent fracture, to strengthen bone and rapidly reduce fracture across the skeleton.

Through its dual mechanism of action, romosozumab rapidly increases BMD at the lumbar spine and hip, starting as early as 6 months; these gains were superior to both alendronate and teriparatide through 12 months of therapy and continued to accrue when transitioned to antiresorptive therapy. Romosozumab rapidly reduced fractures within 12 months. Long-term anti-fracture efficacy also continued after transition to antiresorptive therapy. In summary, romosozumab can benefit patients at high risk for fracture who need a more potent bone-forming agent to rapidly reduce fracture risk.

The key risks with administration of romosozumab are the important identified risks of hypersensitivity and hypocalcemia, and the important potential risks of serious cardiovascular events of myocardial infarction and stroke, osteonecrosis of the jaw (ONJ), and atypical femoral fracture (AFF). An imbalance in myocardial infarction and

stroke was seen in the alendronate-controlled trial within the first year, and was not observed in the larger placebo-controlled study.

Given the totality of the data, the benefit of marked fracture risk reduction in postmenopausal women at high fracture risk is weighed against the possible increased risk of myocardial infarction and stroke, the benefit-risk of romosozumab in postmenopausal women at high risk for fracture is favorable.

Reference should be made to the India-specific prescribing information for further efficacy and safety data on romosozumab.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize safety and tolerability of romosozumab in Postmenopausal women with osteoporosis and a high risk of fracture in India.	• Subject incidence of treatment-emergent adverse events within 12 months. • Subject incidence of treatment-emergent serious adverse events within 12 months. • Change from baseline in laboratory assessments and vital signs at month 12.
Secondary	
• To characterize the efficacy of romosozumab on lumbar spine, total hip, and/or femoral neck BMD in Postmenopausal women with osteoporosis and a high risk of fracture in India.	• Percent change from baseline in BMD (measured by DXA) of the lumbar spine at 6 and 12 months. • Percent change from baseline in BMD (measured by DXA) of the total hip at 6 and 12 months. • Percent change from baseline in BMD (measured by DXA) of the femoral neck at 6 and 12 months.
Exploratory	
CCI [redacted]	

BMD = bone mineral density; and DXA = dual-energy x-ray absorptiometry

4. Study Design

4.1 Overall Design

This multicenter, open-label, single-arm, phase 4 study of romosozumab is part of Amgen's post-marketing requirement to the Central Drugs Standard Control Organization (Indian Regulatory Authority). The study population consists of approximately 100 postmenopausal women subjects in India with osteoporosis and a high risk of fracture for whom romosozumab is indicated in accordance with the approved prescribing information in India. If subject signs the informed consent, then meets the eligibility criteria to receive romosozumab per label and successfully passes the screening process (up to 35 days from the date of informed consent), they will be enrolled at the baseline visit and given the first dose of romosozumab. The enrollment period shall stop once 100 enrolled subjects have received their first dose of romosozumab. A subject will be administered one dose of romosozumab per month at the site for 12 months. Each subject will be followed from the first dose of romosozumab until the end of the 12-month period, death, withdrawal of consent, early discontinuation for any reason, or loss to follow-up (eg, subject transferring to another clinic), whichever occurs first. Treatment-emergent adverse events, and treatment-emergent serious adverse events will be collected during the treatment/observation period and reported for any subject who has received at least 1 dose of romosozumab. Subject incidence of treatment-emergent adverse events and treatment-emergent serious adverse events will be reported and summarized. Treatment efficacy will be determined by percent change from baseline in dual-energy x-ray absorptiometry (DXA) bone mineral density (BMD) of the lumbar spine taken at 6 months, and 12 months for any subject who has a baseline DXA BMD measurement and at least 1 post-baseline DXA BMD measurement at the lumbar spine and received at least 1 dose of romosozumab. All data collected for the purpose of this study will be entered into the electronic case report form (eCRF).

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

Participants in this clinical investigation will be referred to as subjects. For the sample size justification, see Section 9.2.

4.2 Justification for Dose

4.2.1 Justification for Investigational Product Dose

Following the outcome of pivotal clinical studies, romosozumab provided in 105 mg/1.17 mL solution in a single-use prefilled syringe (PFS) was approved by the

India Health Authority to be administered in a full dose of 210 mg in two single-use prefilled syringes subcutaneous (SC) injection once a month for 12 months.

Amgen will supply romosozumab to sites for this study.

4.2.2 Justification for Non-investigational Product Dose

To minimize the risk of hypocalcemia during romosozumab treatment, subjects should be adequately supplemented with calcium (500 to 1000 mg) and vitamin D (600-800 IU) during treatment with romosozumab. Study subjects should obtain calcium and vitamin D per their local means of access to those supplemental medications.

4.3 End of Study

An individual subject is considered to have completed the study if the subject has completed the month 12 study visit shown in the Schedule of Activities. The total study duration for an individual subject is about 13 months (which includes up to 35 days for screening).

The end of study date is defined as the date when the last subject across all sites has completed the assessments for the month 12 study visit stated in the schedule of events.

5. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

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

5.1 Inclusion Criteria

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

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

OR

Subject's legally authorized representative has provided informed consent prior to any study-specific activities/procedures being initiated when the subject has any kind of condition that, in the opinion of the Investigator, may compromise the ability of the subject to give written informed consent.

102 Postmenopausal women with osteoporosis at high risk of fracture at screening that are eligible to receive romosozumab (in accordance with the approved use) in the post-marketing setting in India.

- Postmenopause is defined as no vaginal bleeding or spotting for 12 consecutive months prior to screening.
- High risk of fracture defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

103 Subjects must have at least two vertebrae in the L1 through L4 region and at least one hip are evaluable by DXA, as assessed by the principal investigator, eg, based on lateral spine x-rays.

5.2 Exclusion Criteria

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

201 Subject had previously taken or is currently taking romosozumab or a sclerostin antibody.

202 Subject had myocardial infarction or stroke within a year prior to entering this study.

203 Subject has hypocalcemia during screening as assessed by the central laboratory. Pre-existing hypocalcemia must be corrected prior to initiating therapy with romosozumab.

204 A history of systemic hypersensitivity to romosozumab or to any component of the product formulation.

205 *Use of the following agents affecting bone metabolism*

- Strontium ranelate, or fluoride (for osteoporosis):
  - more than 1 month of cumulative use within 5 years prior to enrollment.
- Intravenous (IV) bisphosphonates.
  - IV Zoledronic acid:
    - any dose received within 3 years prior to enrollment.
    - more than 1 dose received within 5 years prior to enrollment.
  - IV ibandronate or IV pamidronate:
    - any dose received within 12 months prior to enrollment.
    - more than 3 years of cumulative use, unless last dose received ≥ 5 years prior to enrollment.
- Oral bisphosphonates:
  - any dose received within 3 months prior to enrollment.
  - more than 1 month of cumulative use between 3 and 12 months prior to enrollment.
  - more than 3 years of cumulative use, unless last dose received ≥ 5 years prior to enrollment.
- Denosumab or any cathepsin K inhibitor, such as odanacatib (MK-0822):
  - any dose received within 18 months prior to enrollment.
- Teriparatide or any PTH analogs:
  - any dose received within 3 months prior to enrollment.
  - more than 1 month of cumulative use between 3 and 12 months prior to enrollment.
- Systemic oral or transdermal estrogen or SERMs:
  - more than 1 month of cumulative use within 6 months prior to enrollment.
- Hormonal ablation therapy:
  - more than 1 month of cumulative use within 6 months prior to enrollment.
- Tibolone, cinacalcet, or calcitonin:
  - any dose received within 3 months prior to enrollment.
- Systemic glucocorticosteroids:
  - ≥ 5 mg prednisone equivalent per day for more than 14 days within 3 months prior to enrollment.

206 25 (OH) vitamin D levels < 20 ng/mL, as assessed by the central laboratory. Vitamin D repletion will be permitted, and subjects may be rescreened twice (refer to Section 5.5).

207 Subject has any medical condition or illness (acute, chronic, or a history of), which in the opinion of the Investigator might interfere with the evaluation of the safety of the study product or may otherwise compromise the safety of the subject.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

At the discretion of the site physician, the site may consider providing standard of care counseling to the subject on a diet to help supplement calcium and vitamin D during treatment throughout the study.

5.4 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures at the site, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.3).

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

Each subject who enters into the screening period for the study (up to 35 days prior to day 1) 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 throughout the clinical study and must be used on all study documentation related to that subject.

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

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria, prior to the subject receiving the first dose of study drug. The investigator is to document this decision and date, in the subject's medical record and in/on the Subject Enrollment eCRF.

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

5.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study within up to 35 days (screen failure) may be rescreened 2 times at the discretion of the site physician. Refer to Section 8.1.1.

6. Study Intervention

Study intervention is defined as any investigational product(s), non-investigational product(s), placebo, combination product(s), or medical device(s) intended to be administered to a study subject according to the study protocol.

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

A summary of the dosing and administration of each treatment is shown in Table 6-1 below.

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 6-1. Investigational Products

	Amgen Investigational Product:[a]
Study Treatment Name:	romosozumab (EVENITY®)
Dosage Formulation:	105 mg/1.17 mL solution in a single-use prefilled syringe.
Unit Dose Strength:	210 mg QM (Two single-use prefilled syringes)
Route of Administration:	Subcutaneous injection
Accountability:	The dose, start date, start time, stop date, and lot number of romosozumab are to be recorded on each subject's eCRF(s).
Dosing Instructions:	Dose administration should be the last study procedure to complete for each study visit. All subcutaneous injections must be administered by authorized site personnel. The second single-use prefilled syringe must be administered immediately after the first syringe injection is completed. If it is not possible to administer the first dose at the enrollment visit, it must be administered within 72 hours of the enrollment visit date. Day 1 is defined as the date of the first dose. Each monthly dosing visit (post day 1) should be calculated on a consecutive 30-day intervals from the date of the day 1 visit, with a ± 7-day window. In case of an out-of-window dosing visit, romosozumab can be administered ± 2 weeks of the target visit date (calculated on a consecutive 30-day intervals from the date of the day 1 visit). If romosozumab cannot be administered ± 2 weeks of the target visit date, the dose must be considered missed.
Dosage Preparation:	N/A

QM = every month; eCRF = electronic case report form; N/A = not applicable,
[a] Amgen investigational product will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Non-investigational Products

Not applicable.

6.1.3 Medical Devices

The following medical device(s) provided by Amgen for use in this study are listed here.

The romosozumab prefilled syringe is a single-use, disposable, handheld manual injection device for fixed dose SC injection of 2 separate 105 mg/1.17 mL prefilled syringes to administer a total dose of 210 mg of romosozumab in deliverable volume.

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

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

6.1.4 Other Protocol-required Therapies

All other protocol-required drugs (ie, vitamin D and calcium supplements) that are commercially available are not provided by Amgen except under special circumstances (eg, if required by local regulation or due to availability issues). The investigator will be responsible for obtaining supplies of these drugs. Sites will be reimbursed for both calcium and vitamin D supplements.

From screening to end of study, subjects will receive daily calcium and vitamin D supplementation that at a minimum should be in the range of 500 to 1000 mg elemental calcium and 600 to 800 IU vitamin D. In addition, subjects with a serum 25 (OH) vitamin D level of ≥ 20 ng/mL and ≤ 40 ng/mL at screening will receive an initial loading dose of 50,000 to 60,000 IU vitamin D after enrollment, preferably by the oral route. Subjects with a serum 25 (OH) vitamin D level of > 40 ng/mL at screening may also receive the vitamin D loading dose at the principal investigator's discretion. The initial vitamin D loading dose is to be administered within 1 week of the study day 1 visit. However, if the vitamin D loading dose is missed in this timeframe, it should be given as soon as possible thereafter.

Where available, vitamin D3 preparations should be used; if vitamin D3 is not available, use of vitamin D2 preparations is acceptable.

If a subject develops hypercalcemia over the course of the study, the principal investigator may use his/her medical judgment and reduce the calcium and/or vitamin D supplementation to maintain serum calcium concentration within the normal range.

If a subject develops hypocalcemia over the course of the study, appropriate additional supplementation should be instituted as deemed acceptable by local guidelines, to maintain serum calcium concentration within the normal range.

If a subject is unable to tolerate the daily calcium or vitamin D supplementation, the formulation may be changed, or the dose lowered. The intolerance as well as the resolution (ie, change in formulation or dosage) should be documented in the subject chart.

6.1.5 Other Intervention Procedures

This study will require subjects to undergo DXA (lumbar spine, total hip, and femoral neck) at time points specified in the Schedule of Activities (see Section 1.3). Bone mineral density results (absolute BMD measurement and BMD T-scores) will be recorded in the subject's eCRF whenever the subject receives a DXA.

For baseline DXAs (lumbar spine, total hip, and femoral neck): Baseline DXAs can be taken during the screening period (up to 35 days) prior to day 1 to facilitate scheduling for the day 1 visit, or at the day 1 visit.

For month 6 DXAs (lumbar spine, total hip, and femoral neck): The month 6 DXA can be taken at the target date for the month 6 visit (calculated on a consecutive 30-day intervals from the date of the day 1 visit) (± 2 weeks).

For month 12 DXAs (lumbar spine, total hip, and femoral neck): The month 12 DXA can be taken at the target date for the month 12 visit (calculated on a consecutive 30-day intervals from the date of the day 1 visit) (± 2 weeks).

Bone density measurements will be performed by DXA. Only Lunar or Hologic bone densitometers will be allowed for the study. The same DXA machine must be used for all study procedures for a particular subject. All DXA scans will be submitted to and analyzed by the central imaging vendor. A separate procedure manual provided by the central imaging vendor will give specific instructions for acquisition of scans as well as performance of Instrument Quality Control.

For all subjects, bone density will be measured at the lumbar spine and the proximal femur. Lumbar spine scans must include L1 through L4. The left hip should be used for

all scans throughout the study. If the right hip must be used (eg, due to implants) or is inadvertently used at baseline, then it must be used consistently throughout the study.

To be eligible for the study, subjects must have at least two evaluable lumbar vertebrae and one evaluable hip (to be assessed by the Principal Investigator).

6.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors 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(s) associated with an investigational product supplied by Amgen are to be reported.

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

The following treatments, medical devices and/or procedures are prohibited during the study:

- Strontium ranelate, or fluoride (for osteoporosis)
- IV bisphosphonates:
  - IV Zoledronic acid
  - IV ibandronate
  - IV pamidronate
- Oral bisphosphonates
- Denosumab or any cathepsin K inhibitor, such as ondanacatib (MK-0822)
- Teriparatide or any PTH analogs
- Systemic oral or transdermal estrogen or SERMs
- Hormonal ablation therapy
- Tibolone, cinacalcet, or calcitonin
- Systemic glucocorticosteriods (≥ 5 mg prednisone equivalent per day for more than 14 days)

6.2 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding drug-induced liver injury guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.3 Preparation, Handling, Storage, and Accountability

Guidance and information on drug accountability for the investigational product, other protocol-required therapies, and/or device will be provided to the site.

6.4 Treatment Compliance

When subjects are dosed at the site, they will receive romosozumab directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF.

6.5 Treatment of Overdose

Overdose with this product has not been reported. The effects of overdose of romosozumab, and an antidote to overdose are unknown. The maximum amount of romosozumab that can be safely administered in a single dose has not been determined, and there is currently insufficient information to draw any conclusions about the safety of doses higher than those studied in clinical trials. The highest single dose of romosozumab tested in clinical trials is 10 mg/kg SC. Subjects who have received higher than protocol-defined doses should be carefully monitored for adverse events. The injection of higher than protocol-defined doses should be captured and reported as overdose in eCRF which is considered a medication error and must be reported to Amgen (Section 11.4).

6.6 Prior and Concomitant Treatment

6.6.1 Prior Treatment

At screening, record all prior therapies before starting the study that were being taken/used for treating osteoporosis.

For prior therapy being taken for other medical conditions aside from osteoporosis, record history from 5 years before starting the study.

6.6.2 Concomitant Treatment

Throughout the study (from informed consent through the end of study visit), investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care.

For all concomitant therapies, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Section 7.1.

If a patient experiences a myocardial infarction or stroke during treatment with romosozumab in this study, romosozumab should be discontinued.

7.1 Discontinuation of Study Treatment

Subjects (or a legally authorized representative) can decline to continue receiving investigational product and/or other protocol-required therapies and/or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 1-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies and/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.

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

- decision by sponsor
- lost to follow-up
- death
- adverse event
- subject request

- ineligibility determined
- protocol deviation
- non-compliance
- pregnancy

7.2 Subject Discontinuation/Withdrawal From the Study

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 and must document the subject's decision to withdraw in the subject's medical records. Subjects who are withdrawn or removed from treatment or the study will not be replaced.

If a subject withdraws from the study, the subject may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Table 1-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 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

7.3 Lost to Follow-up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible,

3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.

- If the subject continues to be unreachable, the subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator should 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.

8. Study Assessments and Procedures

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

If an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening and Enrollment

The screening date is defined as the date the ICF is signed. Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening window is up to 35 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.5) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 2 times.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 35-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 35 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

Day 1 is defined as the day the first dose of romosozumab is administered. The first dose of romosozumab should be administered as the last study procedure on the day of enrollment. If this is not possible, it must be administered within 72 hours of the enrollment date.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 1-1). Study visits should be scheduled monthly calculated on consecutive 30-day intervals from the date of the day 1 visit date, with a ± 7-day window. In case of an out-of-window study visit, romosozumab can be administered ± 2 weeks of the target visit date (calculated on consecutive 30-day intervals from the date of the day 1 visit). If romosozumab cannot be administered ± 2 weeks of the target visit date, the dose must be considered missed.

8.1.3 Safety Follow-up

Following the Treatment Period, a Month 12 study visit (as shown in the Schedule of Activities) will be performed one month (within ± 7 days) after the end of the last dose of romosozumab. Upon permanent discontinuation from the study for any reason other than completion of all study treatment, an Early Termination Visit (as shown in the Schedule of Activities) will be performed approximately 30 (± 3) days after the end of the last dose of romosozumab.

8.1.4 End of Study

A subject is considered to have completed the study if the subject has completed all the study procedure for the month 12 study visit or Early Termination Visit shown in the Schedule of Activities.

8.2 General Assessments

8.2.1 Informed Consent

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

8.2.2 Demographics

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

8.2.3 Medical History

Any medical history should be documented. Targeted medical history (collected only during screening) should include the following:

- date of diagnosis of postmenopausal osteoporosis
- history of metabolic bone disease
- cardiovascular disease
- chronic kidney disease
- hepatic impairment (Child-Pugh class A, B, or C)
- hypocalcemia (including any other underlying medical history that may predispose to low serum blood calcium)
- hypersensitivities (including drug allergies, environmental allergies, angioedema, anaphylaxis history, rash, dermatitis, and urticaria)
- osteonecrosis of the jaw (including tooth extractions and location of extraction, denture use, jaw pain left or right side)
- atypical femoral fracture (including past hip fractures specify location, hip pain [specify location, ie, lateral side of hip and left or right side])
- smoking status (past and present)

8.2.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

8.2.5 Physical Measurements

Physical measurements will include height and weight. Once the height and weight are entered in the eCRF, the Body Mass Index (BMI) will be calculated and shown in the eCRF.

8.2.6 Substance Abuse History

The targeted medical history (Section 8.2.3) collected at the screening visit will include smoking status (past and present).

8.3 Efficacy Assessments

Dual-energy x-ray absorptiometry BMD measurements on day 1 (baseline), month 6, and month 12.

For baseline DXA: Baseline DXA can be taken during the screening period (up to 35 days) prior to day 1, or at the day 1 visit.

For month 6 DXA: The month 6 DXA can be taken at the target date for the month 6 visit (calculated on a consecutive 30-day intervals from the date of the day 1 visit) (± 2 weeks).

For month 12 DXA: The month 12 DXA can be taken at the target date for the month 12 visit (calculated on a consecutive 30-day intervals from the date of the day 1 visit) (± 2 weeks).

8.4 Safety Assessments

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

8.4.1 Vital Signs

Vital signs collected will include blood pressure, heart rate, respiratory rate, and temperature upon screening.

8.4.2 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. 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. Findings should be recorded on the ECG eCRF.

ECG measurements must be taken by all subjects at the screening visit. Amgen will not provide ECG machines. The site will make available ECG machines per their local means of access.

8.4.3 Clinical Laboratory Assessments

All applicable screening and all on-study blood samples will be processed and sent to the central laboratory.

The central laboratory will be responsible for all screening and on-study serum chemistry, hematology, and serum 25 (OH) vitamin D tests. The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all serum samples.

All blood samples will be obtained by venipuncture before IP administration, when applicable, at the time points outlined in the Schedule of Assessments (Appendix A). The date and time of blood collection will be recorded in the subject's medical record.

Table 11-1 outlines the specific analytes for the serum chemistry and hematology assessments, as well as other assessments to be conducted on blood samples.

When a panic alert is issued for serum calcium, albumin-adjusted calcium levels, phosphorus, or ALP, the sites may perform additional follow-up blood draws for local analysis as required to support subject medical care.

8.4.4 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained.

8.4.5 Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4.

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

8.4.5.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events and is described in Section 11.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through the end of study are reported using the Events eCRF.

8.4.5.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last dose of investigational product (early termination visit) or end of study visit (month 12 visit), whichever occurs first are reported using the Events eCRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator's awareness of the event, as indicated in

Section 11.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

8.4.5.1.3 Serious Adverse Events After the Protocol Required Reporting Period

If the investigator becomes aware of serious adverse events suspected to be related to investigational product after the protocol-required reporting period (as defined in Section 8.4.5.1.2) is complete, then these serious adverse events will be reported to Amgen within 24 hours following the investigator's awareness 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 and handled accordingly based on relationship to investigational product.

If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

8.4.5.1.4 Safety Endpoints that are Study Endpoints

Safety endpoints (treatment-emergent adverse events and treatment-emergent serious adverse events within 12 months of baseline) that are study endpoints are reported on the Events CRF. All endpoints that also meet the criteria of serious adverse event must also be transmitted to safety within 24 hours of the investigator's awareness of the event (refer to Section 11.4).

8.4.5.2 Method of Detecting Adverse Events and Serious Adverse Events

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

8.4.5.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as

discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Events CRF.

8.4.5.4 Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

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

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

8.4.5.5 Safety Monitoring Plan

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

8.4.5.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects will be collected after the start of study treatment and until 3 months after the end of treatment with romosozumab or 3 months after the end of the pregnancy, whichever occurs last.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 11.5. Amgen Global Subject Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events. Further details regarding pregnancy and lactation are provided in Section 11.5.

Pregnancy Testing

Not applicable.

8.5 Pharmacokinetic Assessments

CCI



9. Statistical Considerations

9.1 Statistical Hypotheses

There is no statistical hypothesis for primary endpoint.

9.2 Sample Size Determination

With 100 subjects, there is a 95% chance of observing ≥ 1 adverse event, if the actual event rate is 3% or more.

Also, this study has a 99% power to detect a mean BMD percentage change from baseline of 10% or more in the lumbar spine at month 12 assuming the percent change from baseline of lumbar spine BMD at month 12 has mean 13.1% and standard deviation 5.5% (National Library of Medicine, NCT01575834).

9.3 Populations for Analysis

The following populations are defined:

Population	Description
Full Analysis Set	All subjects who sign the ICF.
Safety Analysis Set	All subjects in the Full Analysis Set who received at least 1 dose of romosozumab.
Efficacy Analysis Set	All subjects in the Full Analysis Set with a baseline and at least 1 postbaseline BMD measurement, and who has received at least 1 dose of romosozumab. The efficacy analysis set may vary for different endpoints due to missing data.

9.3.1 Covariates

No covariates are involved.

9.3.2 Subgroups

No subgroup analysis is planned.

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 4.3.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

Not applicable.

9.4.1.2 Primary Analysis

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

9.4.1.3 Final Analysis

The final analysis will be exactly the same as the Primary Analysis.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

For computation of change from baseline endpoints, baseline will be taken as the observation recorded just prior to first dose of investigational product.

Descriptive statistics will be provided for selected demographics, efficacy, and safety endpoints. Continuous variables will be summarized descriptively using mean, median, standard deviation, 25th percentile, 75th percentile, minimum, maximum, and the number of non-missing observations. Frequencies and percentages will be presented for nominal and ordinal categorical variables.

9.4.2.2 Safety Analyses

9.4.2.2.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	Statistical analyses for safety endpoints are descriptive in nature. Subject incidence of treatment-emergent adverse events, treatment-emergent serious adverse events, fatal adverse events, and adverse events leading to discontinuation from investigational product will be provided. Changes from baseline in vital signs and laboratory

	assessments (serum chemistry and hematology) at month 12 will be summarized. The safety analysis set will be used for these analyses.

9.4.2.2.2 Adverse Events

For the 12-month treatment period, subject incidence of all treatment-emergent adverse events and treatment-emergent serious adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, and adverse events leading to discontinuation from investigational product will also be provided.

9.4.2.2.3 Laboratory Test Results

Actual value by visit and change from baseline by visit will be summarized descriptively for each laboratory parameter. Graphical representation showing central tendency and dispersion of the actual values and/or changes from baseline of laboratory parameters over time will be provided. Laboratory parameters will also be summarized using shifts in laboratory parameters between baseline, and the most extreme post baseline values will be assessed based on the CTCAE v5.0 during the 12-month treatment period.

9.4.2.2.4 Vital Signs

Actual value by visit and change from baseline by visit will be summarized descriptively for each vital sign parameter.

9.4.2.2.5 Exposure to Investigational Product

The exposure to investigational product will be summarized using descriptive statistics.

9.4.2.2.6 Exposure to Concomitant Medication

Concomitant medications will not be summarized.

9.4.2.3 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Secondary	The mean percent change from baseline of lumbar spine BMD at month 12 will be compared with a pre-specified value of 10% using one-sample t-test at 5% two-sided significance level. The mean and 95% CI for percentage change from baseline of lumbar spine, total hip and femoral neck BMD (respectively) at month 6 and 12 will be presented based on t-distribution. The efficacy analysis set will be used for this analysis.

10. References

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11. Appendices

11.1 Appendix 1. List of Abbreviations

Abbreviation	Explanation
AFF	atypical femoral fracture
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMD	Bone mineral density
BUN	blood urea nitrogen
CFR	U.S. Code of Federal Regulations
CRF	Case Report Form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DILI	drug induced liver injury
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
FDA	United States Food and Drug Administration
eCRF	electronic Case Report Form
EDC	electronic data capture
GCP	Good Clinical Practice
GSO	global safety officer
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology
MI	myocardial infarction
NCT	National Clinical Trials
NIH	National Institutes of Health
ONJ	osteonecrosis of the jaw
PFS	Prefilled syringe
PK	pharmacokinetics
RBC	red blood cell
SAP	statistical analysis plan
SC	subcutaneous

US	United States

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 (Analyte listing) will be performed by the central laboratory.

The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all serum samples.

Blood samples for romosozumab levels will be processed by the bioanalytical laboratory.

All blood samples will be obtained by venipuncture before investigative product administration, when applicable, at the time points outlined in the Schedule of Activities (Table 1-1).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 to 5.2.

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

Table 11-1. Central Laboratory Analyte Listing

Laboratory: Chemistry	Laboratory: Hematology	Other Labs
Sodium	RBC	25-OH Vit D
Potassium	Hemoglobin	Romosozumab levels
Chloride	Platelets	
Bicarbonate or CO2	WBC	
Total protein	Differential	
Albumin	• Neutrophils or total neutrophils	
Calcium	• Eosinophils	
Albumin-adjusted calcium	• Basophils	
Magnesium	• Lymphocytes	
Phosphorus	• Monocytes	
Glucose		
BUN or Urea		
Creatinine		
Total bilirubin		
Direct bilirubin		
ALP		
AST (SGOT)		
ALT (SGPT)		

N/A = Not applicable.

If the subject is being followed for possible drug induced liver injury (DILI), the following analytes may be tested at the local laboratory depending on the clinical situation (see Appendix 7 [Section 11.7]).

Table 11-2. DILI Potential Analyte Listing

Chemistry	Total bilirubin, direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT), creatine kinase, ferritin, gamma-glutamyl transferase, haptoglobin
Hematology	Hemoglobin, Platelets, RBC Morphology, RBC Count, WBC Count, WBC Differential
Coagulation	PT, INR, APTT
Immunology	5 Prime Nucleotidase, Alpha-1 Antitrypsin, Antinuclear Antibodies, Anti-Smooth Muscle Antibody, Anti-Soluble Liver Ag/Liver-Pancreas Ag, Cytomegalovirus IgG Antibody, Cytomegalovirus IgM Antibody, Endomysial IgA Antibody, Epstein-Barr Virus EDA IgG Antibody, Epstein-Barr Virus NA IgG Antibody, Epstein-Barr Virus VCA IgG Antibody, Epstein-Barr Virus VCA IgM Antibody, Hepatitis A Virus IgG Antibody, Hepatitis A Virus IgM Antibody, Hepatitis B Core Antibodies, Hepatitis B Core IgM Antibody, Hepatitis B Surface Antigen, Hepatitis B Virus DNA Genotyping, Hepatitis B Virus Surface Antibody, Hepatitis C Antibodies, Hepatitis C Virus RNA Genotyping, Hepatitis D Virus Antibody, Hepatitis D RNA, Hepatitis E RNA, Hepatitis E IgG Antibody, Hepatitis E IgM Antibody, Herpes Simplex Virus Type 1_2 IgG AB, Herpes Simplex Virus Type 1_2 IgM AB, Human Herpes Virus 6 DNA, Human Herpes Virus 7 DNA, Human Herpes Virus 8 DNA, Immunoglobulin G, Liver Kidney AB 1, Parvovirus IgM/IgG Antibody, Serum Caeruloplasmin, Tissue Transglutaminase IgA Antibody, Toxoplasma IgM/IgG, Varicella Zoster Virus Antibody
Toxicology	Acetaminophen

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; DILI = drug-induced liver injury; EDA = early antigen; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; NA = nuclear antigen; PT = prothrombin time; RBC = red blood cell; RNA = ribonucleic acid; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; VCA = viral capsid antigen; WBC = white blood cell

11.3 Appendix 3. Study Governance Considerations

Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

Site staff will identify potential subjects from their existing subject population or may seek referral subjects through existing professional networks or other community sources such as subject advocacy groups. All subject-facing materials must be reviewed/approved by the sponsor and the local IRB/IEC.

Informed Consent Process

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

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

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. 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 informed consent form is to be signed and personally dated by the subject or a legally authorized representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally authorized 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. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 35 days from the previous informed consent form signature date.

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

Data Protection/Subject Confidentiality

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

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

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

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

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

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

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

Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

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

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

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

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or

adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

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

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

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

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

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

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

Source Documents

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

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

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the IRT system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment or certain demographic information, such as gender, race, and ethnicity).

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

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

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

Remote Source Data Review and Verification

If permitted by national and/or local regulations, remote Source Data Review and Verification (rSDR/V) can be implemented. The clinical monitor should be provided with a secure, read-only access to the Electronic Medical Record (EMR) system, including all modules relevant for review. This access should be restricted to the records of only those subjects who participate in the trial and who did not object to remote access to their medical records. A list of the monitors to whom remote access has been granted should be maintained. In order to prevent unauthorized access, access rights should be

revoked once rSDR/V tasks have been completed for the trial. The EMR system should have an audit trail and be able to log information on who accessed data and when. Remote access to the EMR should only be possible using a two-factor authentication.

Study and Site Closure

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

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

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

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.

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

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events will be defined in the Statistical Analysis Plan (SAP).
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an adverse event or serious adverse event.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

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

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording
• When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant adverse event/serious adverse event information in the Event Case Report Form (CRF). • The investigator must assign the following mandatory 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; – assessment of seriousness; – severity (or toxicity defined below); – assessment of relatedness to investigational product(s), other protocol-required therapies, devices, and/or study-mandated activity and/or procedures]; – action taken; and – outcome of event. • If the severity of an adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Event CRF. • It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contact research organization (CRO) in lieu of completion of the Events CRF page. • If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

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

The Common Terminology Criteria for Adverse Events, version 5.0 which is available at the following location:

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

Assessment of Causality

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

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed Events CRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using a paper-based Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event Contingency Report Form) (see Figure 11-1) within 24 hours of the investigator's awareness of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC system has been taken off-line, then the site can report this information on the paper-based Serious Adverse Event Contingency Report Form (see Figure 11-1). • Once the study has ended, serious adverse event(s) will be reported to Amgen (regardless of causality) if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

Figure 11-1. Sample Serious Adverse Event Report Form (paper-based form)

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

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

General Instructions

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

Types of Events to be reported on this form

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

1. **Site Information**

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

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

2. **Subject Information**

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

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

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

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

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

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

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

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

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

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

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

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

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

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

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

4. **Hospitalization**

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

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

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

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

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.

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

6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

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

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

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

A Study # 20210025 EVENITY (romosozumab)	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 ☐ Has been closed for this study

☐ Is not yet available for this study

Amgen India Safety Fax Number: +91-22-6786-9146

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 (Evenity) or an Amgen device (Prefilled Syringe) used to administer the IP? Evenity No✓	Evenity Yes✓	Prefilled Syringe No✓	Prefilled Syringe Yes✓	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No							
				☐Yes ☐No							
				☐Yes ☐No							

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

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

A Study # 20210025 EVENITY (romosozumab)	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✓	 Yes✓	Continuing No✓	 Yes✓	Dose	Route	Freq.	Treatment Med No✓	 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:

Test / Unit / Date Day Month Year											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

A Study # 20210025 EVENITY (romosozumab)	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.		

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

A postmenopausal female is defined as:

- A woman with no menses for 12 months without an alternative medical cause OR
- A woman with no menses for at least 12 months and with a follicle-stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.

All study participants will be postmenopausal females. In the unlikely event a subject becomes pregnant during the study, the investigator will collect and record pregnancy information on the Pregnancy Notification Form (see Figure 11-2).

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through end of study.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through end of study. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (eg, spontaneous abortions, stillbirth, fetal death, congenital anomalies) will be reported as an adverse event or serious adverse event. Note that

an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.

- Any serious adverse event occurring as a result of a poststudy pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment while pregnant (see Section 7.1 for details).

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through end of study.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's awareness of the event.
- Study treatment will be discontinued if female subject breastfeeds during the study.
- With the female subjects signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through end of study.

Figure 11-2. Pregnancy and Lactation Notification Forms

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: 20210025

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
EVENITY (romosozumab)				mm____/dd____/yyyy____

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

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

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

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm____/ dd____/ yyyy____ ☐Unknown ☐N/A

Estimated date of delivery mm____/ dd____/ yyyy____

If N/A, date of termination (actual or planned) mm____/ dd__/ yyyy____

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

If yes, provide date of delivery: mm____/ dd____/ yyyy____

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

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

Amgen Proprietary - Confidential

AMGEN Lactation Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20210025

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
EVENITY (romosozumab)				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

11.6 Appendix 6. Sample Storage and Destruction

Any blood samples collected according to the Schedule of Activities (Table 2-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

Samples can be retained for up to 20 years. 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 [sample types (eg, blood, DXA scan)] 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

Appendix 3 ([Study Governance Considerations]) for subject confidentiality.

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

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

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

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

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

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-1 antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 11-3. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	> 3x ULN (when baseline was < ULN), in the presence of no important alternative causes for elevated AST/ALT and/or TBL values
	OR	
ALP	> 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

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

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen investigational product and other protocol-required therapies, as appropriate is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-3) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

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

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

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 11.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 11-3 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (BIL) (total and direct), and INR within 24 hours
- In cases of TBL > 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 TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels

- A more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- CCI [redacted]
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

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

Approval Signatures

Document Name: Protocol Superseding romosozumab 20210025 Original

Document Description: Superseding Original protocol - India PMR study

Document Number: CLIN-000264199

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Type of Study Protocol: Superseding

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