Summary Table of Study Protocol

Title	Postmarketing Surveillance Study of EVENITY® (Romosozumab) in South Korea
Protocol version identifier	**Superseding** Amendment **2** Version **4**.0
Date of last version of the protocol	**19 September 2023**
EU Post Authorisation Study (PAS) Register No	EUPAS30346
Active Substance	Romosozumab
Medicinal Product	EVENITY®
Product Reference	Not applicable
Procedure Number	Not applicable
Joint PASS	No
Research Question and Objectives	The primary objective of this study is to estimate the incidence rates of adverse events, serious adverse events, and adverse drug reactions among patients receiving EVENITY® on label in the postmarketing setting in South Korea as required by the Ministry of Food and Drug Safety (MFDS). The secondary objective of this study is to investigate the effectiveness of EVENITY® by assessing bone mineral density (BMD), as measured by dual-energy x-ray absorptiometry (DXA), at the lumbar spine and/or total hip and/or femoral neck, as performed per local standard of care. The exploratory objective CCI [redacted]
Country of Study	South Korea
Author	PPD [redacted]

Marketing Authorization Holder

Marketing authorization holder	Amgen Korea Limited 20th Floor, Ferrum Tower, 19, Eulji-ro 5-gil, Jung-gu, Seoul 04539 Republic of Korea +82-2-3434-4800
MAH Contact	Not applicable

Confidentiality Notice

This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staff and members of the Institutional Review Board/Independent Ethics Committee/Institutional Scientific Review Board or equivalent, as applicable.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the research without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: Amgen's general number in the US (1-805-447-1000*);* in South Korea, it is 00798 6113554.

Investigator's Agreement

I have read the attached protocol entitled "Postmarketing Surveillance Study of EVENITY® (Romosozumab) in South Korea", dated **13 November 2023**, and agree to abide by all provisions set forth therein.

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

Signature

Name of Investigator

Date (DD Month YYYY)

Title:

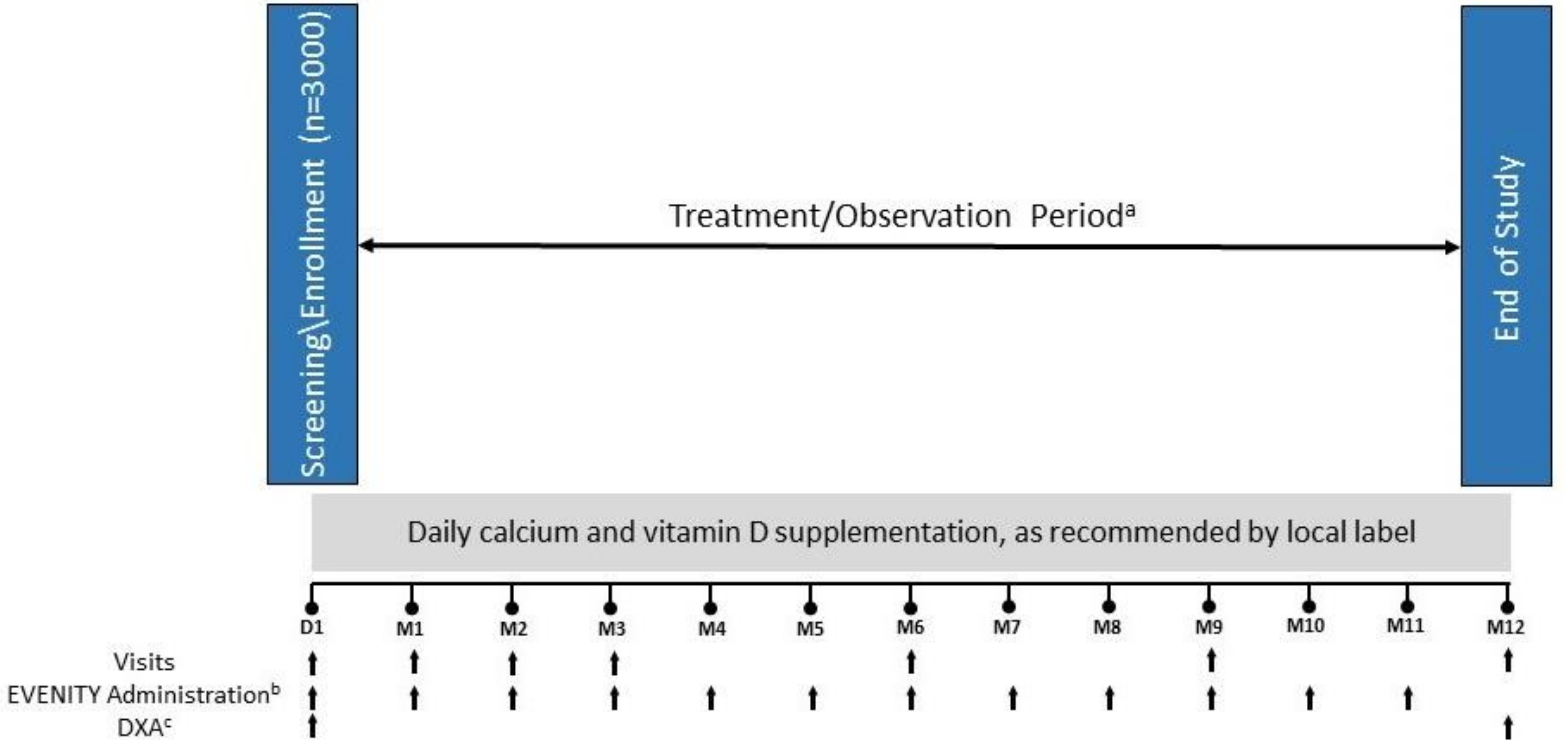
Name of Hospital/Site:

Address/City/State/Country:

Phone Number:

Email:

Study Design Schema



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

[a] Safety events reported by patients spontaneously for up to 30 days after administration of the last dose of EVENITYâ will be collected.
[b] 210 mg subcutaneously.
[c] Collection of baseline DXA results most proximal to the start of EVENITYâ and within the past 12 months. Collection of results whenever the patient receives a DXA during the Treatment/Observation Period but no later than 30 days after the last dose of EVENITYâ).

1. Table of Contents

List of Tables

List of Appendices

2. List of Abbreviations

Abbreviation or Term	Definition/Explanation
ALN	alendronate
BMD	bone mineral density
CI	confidence interval
CKD	chronic kidney disease
CTCAE	Common Terminology Criteria for Adverse Events
D	day
DXA	dual-energy x-ray absorptiometry
eCRF	electronic case report form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EOS	end of study
GFR	glomerular filtration rate
ICF	informed consent form
IRB/IEC	institutional review board/independent ethics committee
M	month
MFDS	Ministry of Food and Drug Safety
PMS	postmarketing surveillance
PTH	parathyroid hormone

3. Responsible Parties

The sponsor of the study is Amgen Korea Limited. The list of investigators will be determined by which sites have access to EVENITY® and can feasibly enroll a reasonable number of patients. Once the list is compiled, the sponsor may provide it upon request.

4. Abstract

- **Study Title**

Postmarketing Surveillance Study of EVENITY® (Romosozumab) in South Korea

- **Study Background and Rationale**

The worldwide prevalence of osteoporosis has been estimated as 200 million people (Reginster and Burlet, 2006). In South Korea, the prevalence of osteoporosis is 38.0% in females aged 50 years and older (Park et al, 2014). Approved treatments for postmenopausal women with osteoporosis include bone resorption inhibitors (Greenblatt, 2005) and bone-forming agents (Canalis, 2010; Papapoulos and Makras, 2008). Despite these advances in osteoporosis therapies, an unmet need remains for patients with significantly compromised bone strength at high risk of fracture.

Romosozumab (EVENITY®) is a humanized monoclonal antibody that is designed to bind and inhibit sclerostin, thereby promoting osteoblast differentiation and activity. By inhibiting sclerostin, EVENITY® has a dual effect on bone, increasing bone formation and decreasing bone resorption.

In Korea, it is mandatory to conduct active pharmacovigilance surveillance as a part of the Risk Management Plan to investigate postmarketing safety and effectiveness in patients treated with newly approved drugs. To comply with this Korean Ministry of Food and Drug Safety (MFDS) regulation, Amgen Limited Korea will conduct a postmarketing surveillance (PMS) study to evaluate the safety and effectiveness of EVENITY® in clinical practice.

Considering the need for progressive osteoporosis treatment options in South Korea and EVENITY®'s current benefit/risk profile, a PMS study of EVENITY® in South Korea will satisfy MFDS regulatory requirements. Amgen will enroll at least 3 000 evaluable patients to collect safety and effectiveness information for the final analysis and

re-examination report, beyond that generated in the registrational EVENITY® study (Study 20150242, approximately 60 subjects) conducted locally.

- **Research Question and Objectives**

Primary Objective

- The primary objective of this study is to estimate the incidence rates of adverse events, serious adverse events, and adverse drug reactions among patients receiving EVENITY® on label in the postmarketing setting in South Korea as required by the MFDS.

Secondary Objective

- The secondary objective of this study is to investigate the effectiveness of EVENITY® by assessing percent change from baseline in bone mineral density (BMD), as measured by dual-energy x-ray absorptiometry (DXA), at the lumbar spine and/or total hip and/or femoral neck, as performed per local standard of care.

Exploratory Objective**s**

The exploratory objectives of this study are:

CCI [redacted]

Hypothesis(es)/Estimation

There is no hypothesis to be tested. Instead, the proposed study will provide descriptive data on use of EVENITY®; the incidence of adverse events and adverse drug reactions; percent change from baseline in BMD at the lumbar spine, and/or total hip, and/or femoral neck; CCI [redacted]; and patient characteristics in the postmarketing setting.

- **Study Design/Type**

This is a prospective, observational, single-arm, multicenter study in patients who are prescribed EVENITY® on label in a postmarketing setting in South Korea.

- **Study Population**

Study enrollment will be offered to patients meeting the eligibility criteria at participating medical sites in South Korea. Enrollment is planned to begin in October 2019 after the launch of EVENITY® in Korea and end after approximately 4.5 years. Patients will be

enrolled on a continuous basis at participating sites, and each will be followed for up to 30 days following their last dose starting from day 1. Investigators are requested to make every effort to enroll the patients in a consecutive enrollment manner until the target number of subjects is reached.

- **Summary of Patient Eligibility Criteria**

Inclusion Criteria

- Patients who are eligible to receive EVENITY® (on label) in the postmarketing setting in South Korea.
- Patients or their authorized representative who consent to participate in this study.

Exclusion Criteria

- Patients currently enrolled in another study involving any investigational procedure, device, or drug.
- Patients who have had prior treatment with EVENITY®.

- **Variables**

Outcome Variables

- Primary outcome **assessment**: Incidence of adverse events, serious adverse events, and adverse drug reactions.
- Secondary outcome **assessment**: Treatment response as determined by percent change from baseline in BMD (measured by DXA) of the lumbar spine and/or total hip and/or femoral neck at M12**, or as close as possible to the last dose of EVENITY® but no later than 30 days after the last dose of EVENITY®**.
- Exploratory outcome **assessment**: CCI [redacted] CCI

- **Study Sample Size**

Per MFDS regulatory requirements, at least 3000 evaluable patients will be enrolled to collect safety and effectiveness information for the final analysis and re-examination report.

- **Data Analysis**

Given the observational nature of the study, data will be summarized descriptively.

The Safety Analysis Set will include all patients who received at least 1 dose of EVENITY® and have at least 1 safety follow-up. The incidence of adverse events will be

summarized to include all treatment-emergent adverse events recorded from the start of EVENITY® on this study or any worsening of medical conditions initially experienced before initiation of this study. This summary for adverse events will be performed for the following categories:

- all adverse events and adverse drug reactions
- serious adverse events and serious adverse drug reactions
- adverse events leading to EVENITY® discontinuation
- fatal events

The incidence of adverse events of interest will be presented, and the 95% CI for the incidence estimate using an exact method will be provided.

The Effectiveness Analysis Set will include all patients with a baseline and at least 1 postbaseline BMD measurement at the lumbar spine and/or total hip and/or femoral neck. The effectiveness analysis includes the following:

- Percent change (%) in BMD from baseline at M12 **or as close as possible to the last dose of EVENITY® but no later than 30 days after the last dose of EVENITY®** at lumbar spine.
- Percent change (%) in BMD from baseline at M12 **or as close as possible to the last dose of EVENITY® but no later than 30 days after the last dose of EVENITY®** at total hip.
- Percent change (%) in BMD from baseline at M12 **or as close as possible to the last dose of EVENITY® but no later than 30 days after the last dose of EVENITY®** at femoral neck.

CCI

[redacted]

5. Amendments and Updates

Amendment or Update No.	Date	Section of Study Protocol	Amendment or Update	Reason
Original	29 November 2018	Not applicable		
1	04 November 2021	See summary of changes		
2	**19 September 2023**	**See summary of changes**		
Superseding amendment 2	**13 November 2023**	**See summary of changes**		

6. Milestones

Milestone	Planned date
Start of data collection	Q4 2019
End of data collection	Q2 2025
Periodic report 1-1	Q4 2019
Periodic report 1-2	Q2 2020
Periodic report 2-1	Q4 2020
Periodic report 2-2	Q2 2021
Periodic report 3	Q2 2022
Periodic report 4	Q2 2023
Periodic report 5	Q2 2024
Registration in the EU PAS register	Prior to first subject enrolled
Final report of study results	Q3 2025

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Disease State/Therapeutic Area

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture (NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001). Osteoporosis is a common disorder; according to the World Health Organization's current definition of osteoporosis (bone mineral density [BMD] T-score $\geq$ 2.5 standard deviations below the mean for normal young adults) (World Health Organization, 1994), the worldwide prevalence of osteoporosis has been estimated as 200 million people (Reginster and Burlet, 2006). In South Korea, the prevalence of osteoporosis is 38.0% in females aged 50 years and older (Park et al, 2014). The morbidity and mortality associated with osteoporosis-related fractures is significant in terms of disability

to an individual and cost to the global economy (Cree et al, 2003; Kanis et al, 2001a; Kanis et al, 2001b).

Approved treatments for postmenopausal women with osteoporosis include inhibitors of bone resorption, such as selective estrogen receptor modulators (SERMs, eg, raloxifene), bisphosphonates (eg, alendronate [ALN], risedronate, ibandronate, and zoledronic acid), calcitonin, the RANKL inhibitor denosumab, or agents that stimulate bone formation like teriparatide (the 1-34 fragment of intact parathyroid hormone [PTH]) (Greenblatt, 2005). Antiresorptive therapies prevent osteoclasts from resorbing bone, slowing the progression of bone breakdown, increasing BMD, and lowering the risk of vertebral fractures (relative risk reduction [RRR]: 40% to 70%) and, to a lesser extent, nonvertebral fractures (RRR: 20% to 25%) (Cummings et al, 2009; Black et al, 2007; Chestnut et al, 2004; McClung et al, 2001; Chestnut et al, 2000; Ettinger et al, 1999; Harris et al, 1999; Cummings et al, 1998; Black et al, 1996).

In contrast, bone-forming agents can promote larger improvements in bone mass and bone strength than antiresorptives and restore bone architecture, thereby addressing the need for improved protection against fractures, in particular at nonvertebral sites (Canalis, 2010; Papapoulos and Makras, 2008). Analogs of PTH (PTH 1-34 [teriparatide] and PTH 1-84) increase bone remodeling by stimulating both bone formation and bone resorption with a net gain in bone mass. As a result, there is a marked improvement in BMD, as well as indices of bone microstructure that are associated with improved mechanical strength (Borggrefe et al, 2010). Teriparatide lowers the risk of one or more new vertebral fractures by 65% (Neer et al, 2001) as well as nonvertebral fractures by approximately 35% to 50%. Parathyroid hormone treatment, however, are associated with some disadvantages, including standard daily injections, limitation of use for a maximum of 2 years, and a theoretical risk for osteosarcoma (Forteo USPI).

Despite these advances in osteoporosis therapies, an unmet need remains for patients with significantly compromised bone strength at high risk of fracture.

Product Background

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

resistant to fractures (Hamersma et al, 2003; Vanhoenacker et al, 2003). Administration of a sclerostin antibody, resulting in the blocking of the inhibitory effect of sclerostin on bone formation, has been shown to increase bone formation, BMD, and bone strength in multiple animal models (normal and osteoporotic rats, monkeys) (Ominsky et al, 201**1**; Ominsky et al, 2010; Li et al, 2009; Li et al, 2007a; Li et al, 2007b).

Romosozumab (EVENITY®) is a humanized monoclonal antibody that is designed to bind and inhibit sclerostin, thereby promoting osteoblast differentiation and activity. By inhibiting sclerostin, EVENITY® has a dual effect on bone, increasing bone formation and decreasing bone resorption. EVENITY® increases trabecular and cortical bone mass and improves bone structure and strength.

Proof of biological activity for EVENITY® has been established in a first-in-human, ascending-single-dose study in healthy men and postmenopausal women, an ascending-multiple-dose study in healthy men and postmenopausal women with low bone mass, and a phase 2 dose-ranging study in postmenopausal women with low bone mass. In all studies, treatment with EVENITY® was generally well-tolerated and resulted in a transient increase of the bone formation markers Procollagen Type 1 N-telopeptide, Osteocalcin, and Bone-Specific Alkaline Phosphatase, and a decrease in the bone resorption marker serum type‑1 collagen C‑telopeptide. Increases in BMD at the lumbar spine, total hip, and femoral neck have also been demonstrated by dual-energy x-ray absorptiometry (DXA) and quantitative computed tomography (QCT).

Comprehensively, 19 clinical studies have been completed; key phase 3 studies include the following:

- A phase 3 study in postmenopausal women with osteoporosis randomized to either 12 months of EVENITY® or placebo followed by denosumab for 24 months in each group
- A phase 3 study in postmenopausal women with osteoporosis to evaluate the noninferiority of EVENITY® at a 90 mg/mL concentration compared with a 70 mg/mL concentration
- A phase 3 study to compare the efficacy and safety of EVENITY® with placebo in men with osteoporosis
- A phase 3 fracture study in postmenopausal women with osteoporosis randomized to EVENITY® for 12 months followed by ALN treatment compared to ALN treatment alone
- A phase 3 study in postmenopausal Korean women with osteoporosis randomized to either EVENITY® or placebo for 6 months

In the phase 3 pivotal fracture trials, EVENITY® significantly increased BMD across all key skeletal sites as early as 6 months and reduced the incidence of new vertebral fractures in postmenopausal women with osteoporosis (FRAME and ARCH study) (Cosman et al, 2016; Saag et al, 2017). In addition, non-vertebral and hip fractures were reduced in patients taking EVENITY® compared to ALN, the most widely used bisphosphonate (ARCH study; Saag et al, 2017).

7.2 Rationale

In Korea, it is mandatory to conduct active pharmacovigilance surveillance as a part of the Risk Management Plan to investigate postmarketing safety and effectiveness in patients treated with newly approved drugs. To comply with this Korean Ministry of Food and Drug Safety (MFDS) regulation, Amgen Limited Korea will conduct a PMS study to evaluate the safety of EVENITY® in clinical practice.

Considering the need for progressive osteoporosis treatment options in South Korea and EVENITY®'s current benefit/risk profile, a PMS study of EVENITY® in South Korea will satisfy MFDS regulatory requirements. Amgen will enroll at least 3 000 evaluable patients to collect safety and effectiveness information for the final analysis and re-examination report. The findings also will provide additional safety and effectiveness data beyond that generated in the registrational EVENITY® study (Study 20150242, approximately 60 subjects) conducted locally.

7.3 Statistical Inference (Estimation or Hypothesis[es])

This PMS is a prospective, observational, multicenter study in patients who are being treated with EVENITY®. There is no hypothesis to be tested. Instead, the proposed study will provide descriptive data on use of EVENITY®; the incidence of adverse events and adverse drug reactions; percent change from baseline in BMD at the lumbar spine, and/or total hip, and/or femoral neck **at M12 or as close as possible to the last dose of EVENITY® but no later than 30 days after the last dose of EVENITY®**; CCI [redacted] and patient characteristics in the postmarketing setting.

8. Research Question and Objectives

8.1 Primary

According to local regulation, a PMS study is required for new medicines approved in South Korea to collect safety and effectiveness data in routine clinical practice. A prospective, observational, single-arm, multicenter study design is chosen to meet the postmarket surveillance guidelines from the MFDS in South Korea.

The primary objective of this study is therefore to estimate the incidence rates of adverse events, serious adverse events, and adverse drug reactions among patients receiving EVENITY® on label in the postmarketing setting in South Korea as required by the MFDS.

8.2 Secondary

The secondary objective of this study is to investigate the effectiveness of EVENITY® by assessing percent change from baseline in BMD, as measured by DXA, at the lumbar spine, and/or total hip, and/or femoral neck, as performed per local standard of care.

8.3 Exploratory

The exploratory objective**s** of this study **are:**

CCI [redacted]

9. Research Methods

9.1 Study Design

This is a prospective, observational, single-arm, multicenter study in patients who are prescribed EVENITY® on label in a postmarketing setting in South Korea.

If patients meet the eligibility criteria (Section 9.2.3) and sign the informed consent, they will be enrolled. Patients will be seen by their physician per local standard of care and receive EVENITY® on label. Adverse events, serious adverse events, and adverse drug reactions reported by patients spontaneously from the first dose of EVENITY® to 30 days after the administration of the last dose will be collected and reported. CCI [redacted]

[redacted] Treatment response will be determined by percent change from baseline in BMD (measured by DXA) of the lumbar spine, and/or total hip, and/or femoral neck at M12**, or as close as possible to the last dose of EVENITY® but no later than**

30 days after the last dose of EVENITY®. CCI [redacted]

The enrollment period will stop when the enrolled sample size is at least 3000 evaluable patients. Each patient will be followed from the first dose of EVENITY® to no later than 30 days after their last dose, death, withdrawal of consent, or loss to follow-up (eg, patients transferring to another clinic), whichever occurs first.

For a full list of study procedures, including the timing of each procedure, please refer to the Schedule of Assessments in Table 9-1.

Table 9-1. Schedule of Events

	Screening/Enrollment (Start of EVENITY®)	Treatment/Observation Visits (Treatment/Observation Period, Early Termination Visit)						
Data Collection	Screening[a]	Day 1[a]	M1	M2	M3	M6	M9	EOS (~M12)[e]
Eligibility	X	-	-	-	-	-	-	-
Informed consent	X	-	-	-	-	-	-	-
Physical measurements (height, weight)	X	-	-	-	-	-	-	-
Vital signs (blood pressure)	X	-	-	-	-	-	-	-
Demographic data[b]	X	-	-	-	-	-	-	-
DXA of lumbar spine (and/or femoral neck, and/or total hip)[c]	X[d]	-	-	-	-	-	-	X[f]
CCI								
Medical history	X	-	-	-	-	-	-	-
Targeted medical history[h]	X	-	-	-	-	-	-	-
eCRF collection of serum calcium and 25(OH) vitamin D standard-of-care labs from patient chart[i]	X	-	-	-	-	-	-	-
Concomitant medications with indication[j]	X	-	X	X	X	X	X	X
Reportable events collection[k]	-	X ◄	———	———	———	———	———	► X
Treatment with EVENITY®	-	X ◄	———	———	———	———	———	► -
CCI								

Footnotes defined on next page

BMD = bone mineral density; CA = calcium; DXA = dual-energy x-ray absorptiometry; eCRF = electronic case report form; EOS = end of study; M = month

[a] Screening and day 1 can take place on the same day.

[b] Sex, age, race, and ethnicity.

[c] Most recent DXA date, body site, and result (BMD results [absolute BMD measurement and BMD T-scores]) whenever the patient receives a DXA.

[d] DXA results most proximal to start of EVENITYâ and within past 12 months.

[e] EOS defined as 30 days after the last dose of EVENITY®. No data should be collected after this timepoint.

[f] DXA results at M12 or as close as possible to the last dose of EVENITY® but no later than 30 days after the last dose **of EVENITY®**.

CCI

[h] Includes the following:

- Date of diagnosis of postmenopausal osteoporosis
- History of metabolic bone disease
- Fracture history (including date of diagnosis and number of fractures)
  - vertebral
  - nonvertebral
  - hip
- 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, 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)

[i] Laboratory values most proximal to start of EVENITY® and within past 6 months.

[j] Includes the following:

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

[k] Includes adverse events, serious adverse events, other safety findings, and spontaneously reported product complaints. All reportable events by patients spontaneously from the time of first dose until up to 30 days after administration of final dose of EVENITY® will be collected. Safety events will be reported as data becomes available.

CCI

9.2 Setting and Study Population

9.2.1 Study Period

Enrollment is planned to begin in October 2019 after the launch of EVENITY® in Korea and end after approximately 4.5 years. Patients will be enrolled on a continuous basis at participating sites, and each will be followed for up to 30 days following their last dose starting from day 1.

9.2.2 Selection and Number of Sites

Study sites will include approximately 60 sites that have postmarket use of EVENITY®.

9.2.3 Patient/Healthcare Professional Eligibility

9.2.3.1 Inclusion Criteria

- Patients who are eligible to receive EVENITY® (on label) in the postmarketing setting in South Korea.
- Patients or their authorized representative who consent to participate in this study.

9.2.3.2 Exclusion Criteria

- Patients currently enrolled in another study involving any investigational procedure, device, or drug.
- Patients who have had prior treatment with EVENITY®.

9.3 Variables

9.3.1 Outcome Assessment

9.3.1.1 Primary Endpoint

The primary endpoint is incidence of adverse events and adverse drug reactions (including seriousness and causality to drug), inclusive of local injection site reactions, throughout the treatment/observation period for any patient who has received at least 1 dose of EVENITY® and complete at least 1 safety follow-up. Patient incidence of the adverse events will be reported and summarized.

9.3.1.2 Secondary Endpoint

The secondary endpoint is treatment response as determined by percent change from baseline in BMD (measured by DXA) of the lumbar spine and/or total hip and/or femoral neck at M12, **or as close as possible to the last dose of EVENITY® but no later than 30 days after the last dose of EVENITY®**.

9.3.1.3 Exploratory Endpoint

CCI

[redacted]

9.3.2 Validity and Reliability

Efforts will be made to collect complete data through the use of clear instructions to investigators regarding the completion of eCRFs.

9.4 Data Sources

The data source for this study is subject medical chart notes. These notes may include a combination of paper and electronic records. Study site staff will extract data from the subject notes into the study-specific electronic database provided by the sponsor. No patient data will be collected beyond 30 days after their last dose.

9.5 Study Size

Per MFDS request, at least 3 000 evaluable patients will be enrolled to collect adequate safety and effectiveness information for the final analysis and re-examination report. To be considered evaluable, a patient must sign the study specific informed consent form (ICF) after the site contract has been executed, receive at least 1 dose of EVENITY® (with use per the approved label), and complete at least 1 safety follow-up (conducted via telephone or in office).

9.6 Data Management

9.6.1 Obtaining Data Files

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and available upon request.
- Updates to eCRFs will be automatically documented through the software's audit trail.

9.6.2 Linking Data Files

Not applicable.

9.6.3 Review and Verification of Data Quality

Automatic checks within the database and further manual review by the sponsor will help to ensure quality and completeness of the data. During this review, patient data is checked for consistency, omissions, and any apparent discrepancies. Data queries will be sent to sites for clarification and resolution of discrepancies.

9.7 Data Analysis

9.7.1 Planned Analyses

According to local regulations, interim analyses will be performed for periodic reporting. Periodic reports are submitted to MFDS every 6 months for the first 2 years and every year thereafter until the end of study period.

9.7.1.1 Final Analysis

The final analysis will be conducted for the re-examination report after all the study data are collected and cleaned.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

The statistical analysis in this PMS study will be descriptive in nature, and no hypothesis testing will be performed. Categorical outcomes will be summarized by the number and percentage of subjects in each category. Continuous outcomes will be summarized by the number of nonmissing values, mean, standard deviation, median, lower and upper quartiles, and minimum and maximum values. For the incidence of adverse events and adverse drug reactions, 95% CI will be presented based on an exact method.

For subjects who are prematurely withdrawn, reasons for withdrawal will be described.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Patients may have missing data points for a variety of reasons. Data may be missing due to patient's early withdrawal from study, a missed visit, or nonevaluability of an endpoint at a particular time point. In general, analyses will be based on available data. Sensitivity analyses may be conducted using different approaches to handle missing data. Missing baseline or postbaseline BMD data will not be imputed.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Patient Characteristics

Demographic and baseline characteristics collected will be tabulated descriptively.

9.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

9.7.2.4.1 Analysis of the Primary Endpoint

The Safety Analysis Set will include all patients who received at least 1 dose of EVENITY® and complete at least 1 safety follow-up. The incidence of adverse events and adverse drug reactions will be summarized to include all treatment-emergent adverse events recorded from the start of EVENITY® on this study or any worsening of medical conditions initially experienced before initiation of this study. This summary for adverse events will be performed for the following categories:

- all adverse events and adverse drug reactions
- serious adverse events and serious adverse drug reactions
- adverse events leading to EVENITY® discontinuation
- fatal events

The incidence of adverse events of interest will be presented, and the 95% CI for the incidence estimate using an exact method will be provided.

9.7.2.4.2 Analysis of the Secondary Endpoint

The Effectiveness Analysis Set will include all patients with a baseline and at least 1 postbaseline BMD measurement at the lumbar spine and/or total hip and/or femoral neck. The effectiveness analysis includes the following:

- Percent change (%) in BMD from baseline at M12 **or as close as possible to the last dose of EVENITY® but no later than 30 days after the last dose of EVENITY®** at lumbar spine.
- Percent change (%) in BMD from baseline at M12 **or as close as possible to the last dose of EVENITY® but no later than 30 days after the last dose of EVENITY®** at total hip.
- Percent change (%) in BMD from baseline at M12 **or as close as possible to the last dose of EVENITY® but no later than 30 days after the last dose of EVENITY®** at femoral neck.

Data will be summarized in a periodic PMS report filed annually per local regulation.

9.7.2.4.3 Analysis of the Exploratory Endpoint

CCI

[redacted]

CCI

[redacted]

9.7.2.5 Sensitivity Analysis

9.7.2.5.1 Subgroup Analysis

The primary and secondary endpoints will be analyzed by the following subgroups if appropriate:

- **sex (male, female)**
- age at baseline (years):
  - < 65 years
  - ≥ 65 - 75 years
  - ≥ 75 years
- history of osteoporosis therapy use (prior and/or concomitant bisphosphonate or other treatment use)
- renal function at baseline (stage of chronic kidney disease [CKD] based on estimated glomerular filtration rate [GFR]):
  - CKD 1: GFR ≥ 90 mL/min/1.73 m^2
  - CKD 2: 89 to 60 mL/min/1.73 m^2
  - CKD 3: 59 to 30 mL/min/1.73 m^2
  - CKD 4: 29 to 15 mL/min/1.73 m^2
  - CKD 5: < 15 mL/min/1.73 m^2
  - **CKD 1-3: GFR ≥ 30 mL/min/1.73 m^2**
  - **CKD 4-5: GFR ≤ 29 mL/min/1.73 m^2**
- **hepatic impairment at baseline (Child-Pugh class A, B, or C)**
- **concurrent diseases (Yes or No)**
- **concomitant medication (Yes or No)**
- **dose of EVENITY® (Full treatment [received 12 doses of EVENITY®] or Partial treatment [received less than 12 doses of EVENITY®])**

These subgroups will be re-examined for appropriateness and may be re-categorized or omitted (due to small sample size, for example, if there are < 10% of subjects within a subgroup).

9.8 Quality Control

The Amgen representative(s) and regulatory authority inspectors are responsible for inspecting the various records of the study (eg, eCRFs and other pertinent data) provided that patient confidentiality is respected.

Amgen or its designee is responsible for verifying the eCRFs to verify adherence to the protocol, completeness, accuracy, and consistency of the data and adherence to local regulations on the conduct of PMS studies.

The investigator agrees to cooperate with Amgen or contract research organization (CRO) staff to ensure that any problems detected in the course of the study, including delays in completing eCRFs, are resolved.

In accordance with the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Quality, Compliance, and Audit function (or designees).

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Error(s)/Misclassification(s)

As with any surveillance study that relies on data entry from multiple sites, there is the potential for misclassifying adverse events and adverse drug reactions (including seriousness and causality). Misclassifications can impact the validity of outcomes as well as affect overall conclusions.

9.9.1.2 Information Bias

Missing or incomplete data is a potential risk for information bias and efforts will be made to collect complete data through the use of clear instructions to investigators regarding the completion of eCRFs.

There is no systematic review or systematic method of adverse event collection. Adverse events are collected as part of a regular interaction with the patient as would be in normal practice. Therefore, adverse events collected are subject to reporting bias, but such effect is inherent to real-world surveillance.

9.9.1.3 Selection Bias

Not applicable.

9.9.1.4 Confounding

It is very likely that patients enrolled in this study (ie, patients with osteoporosis who receive EVENITY®) are more severely diseased than patients with osteoporosis who do not receive EVENITY® (and thus are not included in the study). The confounding by indication bias leading to the inability of safety and efficacy results to be generalized to the larger population is not relevant because the indication per label applies to patients at high risk for fracture. Further, patients with severe osteoporosis may not necessarily receive a repeat DXA scan, as it would not change disease management. The lack of follow-up data in the most severely diseased population may therefore lead to some confounding in the results.

9.9.2 External Validity of Study Design

DXA scans for BMD are only covered once per year by insurance. As such, inadequate or lack of BMD data could impact the breadth of data necessary to make generalizations about the source population.

9.9.3 Limitations Due to Missing Data and/or Incomplete Data

Some patients may discontinue the study, creating missing or incomplete data for the study endpoint assessments. Such discontinuations may be related or informative to the outcomes. Consequently, there is a risk for bias and lack of robust data to analyze results.

9.10 Other Aspects

9.10.1 Language

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

10. Protection of Human Subjects

10.1 Informed Consent

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

Before a patient can participate in the study, the investigator or his/her delegated representative is responsible for obtaining written informed consent, from the patient or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific

activities/assessments are conducted. A legally acceptable representative is an individual or other body authorized under applicable law to consent on behalf of the patient, to the patient's participation in the clinical trial.

The acquisition of informed consent is to be documented in the patient's medical records, and the ICF is to be signed and personally dated by the patient or legally acceptable representative and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed ICF is to be provided to the patient or legally acceptable representative.

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

10.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

A copy of the protocol, proposed ICF, other written patient information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and ICF must be received by Amgen before the study can be executed. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse event(s) occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures. The investigator is responsible for obtaining annual IRB approval and IRB/IEC renewal throughout the duration of the study. Copies of the investigator's reports, where applicable by local regulations and the IRB/IEC continuance of approval must be sent to Amgen.

Any protocol amendments will be submitted to the local IRB for their review and approval. Annual IRB approval/renewal throughout the duration of the study will be obtained and copies of the IRB continuance of approval will be sent to Amgen.

10.3 Patient Confidentiality

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

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

In compliance with local country regulations, 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 patient's original medical records for verification of study-related activities 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 patient to permit such individuals to have access to his/her study-related records, including personal information.

10.4 Subjects Decision to Withdraw

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

Withdrawal of consent for a study means that 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 steps for withdrawal of their consent from the study.

11. Collection, Recording and Reporting of Safety Information and Product Complaints

Date of Awareness ("day 0"): For the purposes of Amgen's regulatory reporting, the date of awareness is the date that investigator first becomes aware of information that constitutes a Reportable Event (ie, the date, the fax, mail, or telephone call is received by investigator). This date must be captured by the investigator and clearly communicated or recorded on any safety information transmitted to Amgen.

11.1 Definition of Reportable Events

11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

An adverse drug reaction is a noxious and unintended response to a pharmaceutical product(s) administered normally.

Adverse Device Effect

An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

11.1.2 Serious Adverse Events/Serious Adverse Device Effects

A serious adverse event is any adverse event/serious adverse device effect as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other medically important serious event" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other medically important serious event" refer**s** to important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse event) include:

- Medication errors, overdose/underdose, whether accidental or intentional, misuse, addiction, or abuse, involving an Amgen product,
- Use of an Amgen product while pregnant and/or breastfeeding,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Accidental or Occupational exposure,
- Any lack or loss of intended effect of the product(s).

11.1.4 Product Complaints

Product Complaints include any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors and partners for whom Amgen manufactures the material. This includes any drug(s), device(s), or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes EVENITY® and prefilled syringe.

11.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting information from patients prospectively. All reportable events (adverse events, product complaints, and other safety findings) considered to have occurred following subject exposure to EVENITY® will be collected from the time of first dose to 30 days after administration of final dose of EVENITY®. The investigator is responsible for ensuring that all reportable events they become aware of during study period**,** are recorded in the patient's appropriate study documentation. It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen. 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. All reportable events must be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within the timelines stated in Table 9.2 below.

Table 9-2. Types of Safety Data to be Collected and Reported in Primary Data Collection Studies Collecting All Reportable Events

Reportable Events/Event Type	*Reporting Timeframe
• Serious Adverse Events (related and non-related) • Product Complaints (serious and non-serious) • Other Safety Findings (serious and non-serious) • Pregnancy and/or Lactation Exposure	• Within 1 business day from when investigator first becomes aware of the event
• Non-serious Adverse Events (related and non-related)	• Within 15 calendar days from when investigator first becomes aware of the event

* Please note, more stringent reporting timelines may apply per local requirements

See Appendix B for sample Safety Reporting Form(s), Appendix C for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix D for sample Pregnancy and Lactation Notification Forms.

The investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded in the study documentation where safety data may also be recorded.

11.2.1 Collection of Pregnancy and Lactation Information

Female Subjects Who Become Pregnant

The investigator will collect pregnancy information on any female subject who becomes pregnant following exposure to EVENITY® through an additional 3 months.

Information will be recorded on the Pregnancy Notification Form (see Appendix D). The worksheet must be submitted to Amgen Safety within 1 business day of when investigator first becomes aware of the subject's pregnancy (Note: investigator is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide investigator with a consent form and questionnaire to collect additional information. 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 following exposure to EVENITY® through an additional 3 months. This information will be forwarded to Amgen 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 Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is considered another safety finding, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.

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

Male Subjects with Partners who Become Pregnant [or Were Pregnant at the Time of Enrollment]

In the event a male subject fathers a child following exposure to EVENITY®, and for an additional 3 months after discontinuing EVENITY®, the information will be recorded on the Pregnancy Notification Form. The form (see Appendix D) must be submitted to Amgen Safety within 1 business day of when the investigator first becomes aware of the pregnancy. (Note: investigator is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide investigator with a consent form and questionnaire to collect additional information. The investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.

After obtaining the female partner's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Safety.

Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of the pregnancy will be reported to Amgen Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

The investigator will collect lactation information on any female subject who breastfeeds while taking EVENITY® through an additional 3 months.

Information will be recorded on the Lactation Notification Form (see Appendix D) and submitted to Amgen Safety within 1 business day of when the investigator's first becomes aware of the lactation exposure.

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 EVENITY® through an additional 3 months after discontinuing EVENITY®.

11.2.2 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, investigators/institutions, IRBs/IECs or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of serious adverse events in accordance with local procedures and statutes.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the contractual 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.

13. Plans for Disseminating and Communicating Study Results

Interim results will be included in the periodic reports that will be provided to the MFDS. The final report will also be provided to the MFDS in an application for re-examination.

13.1 Publication Policy

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

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

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

14. Compensation

Not applicable.

15. References

Balemans W, Ebeling M, Patel N, et al. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). *Hum Mol Genet*. 2001;10(5):537-543. **doi:10.1093/hmg/10.5.537**

Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356(18):1809-1822. **doi:10.1056/NEJMoa067312**

Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet*. 1996;348:1535-1541. **doi:10.1016/s0140-6736(96)07088-2**

Borggrefe J, Graeff C, Nickelsen TN, Marin F, Glüer CC. Quantitative computed tomographic assessment of the effects of 24 months of teriparatide treatment on 3D femoral neck bone distribution, geometry, and bone strength: results from the EUROFORS study. *J Bone Miner Res*. 2010;25(3):472-481. **doi:10.1359/jbmr.090820**

Brunkow ME, Gardner JC, Van Ness J, et al. Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. *Am J Hum Genet*. 2001;68(3):577-589. **doi:10.1086/318811**

Canalis E. Update in new anabolic therapies for osteoporosis. *J Clin Endocrinol Metab*. 2010;95(4):1496-1504. **doi:10.1210/jc.2009-2677**

Chestnut III CH, Skag A, Christiansen C, et al. Effects of oral Ibandronate administered daily or intermittently on fracture risk in postmenopausal Osteoporosis. *J Bone Miner Res*. 2004;(8):1241-1249. **doi:10.1359/JBMR.040325**

Chestnut III CH, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study (PROOF). PROOF Study Group. *Am J Med*. 2000;109:267-276. **doi:10.1016/s0002-9343(00)00490-3**

Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;375(16):1532-1543. **doi:10.1056/NEJMoa1607948**

Cree MW, Juby AG, Carriere KC. Mortality and morbidity associated with osteoporosis drug treatment following hip fracture. *Osteoporos Int*. 2003;14(9):722-727. **doi:10.1007/s00198-003-1430-3**

Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361(8):756-765. **doi:10.1056/NEJMoa0809493**

Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA*. 1998;280(24):2077-2082. **doi:10.1001/jama.280.24.2077**

Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA*. 1999;282(7):637-645. **doi:10.1001/jama.282.7.637**

FORTEO (teriparatide injection) for subcutaneous use **[prescribing information]**. Indianapolis, IN: Eli Lilly and Company; March 2017.

Greenblatt D. Treatment of postmenopausal osteoporosis. *Pharmacotherapy*. 2005;25(4):574-584. **doi:10.1592/phco.25.4.574.61031**

Hamersma H, Gardner J, Beighton P. The natural history of sclerosteosis. *Clin Genet*. 2003;63(3):192-197. **doi:10.1034/j.1399-0004.2003.00036.x**

Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA*. 1999;282(14):1344-1352. **doi:10.1001/jama.282.14.1344**

Kanis JA, Dawson A, Oden A, Johnell O, De Laet C, Jonsson B. Cost-effectiveness of preventing hip fracture in the general female population. *Osteoporosis Int*. 2001a;12**(5)**:356-362. **doi:10.1007/s001980170102**

Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. *Osteoporosis Int*. 2001b;12**(5)**:417-427. **doi:10.1007/s001980170112**

Li X, Ominsky MS, Warmington KS, et al. Sclerostin antibody treatment increases bone formation, bone mass, and bone strength in a rat model of postmenopausal osteoporosis. *J Bone Miner Res*. 2009;24(4):578-588. **doi:10.1359/jbmr.081206**

Li X, Warmington KS, Niu Q, et al. **Treatment with an anti-sclerostin antibody increased** bone formation without increasing bone resorption in aged male rats. *J Bone Miner Res*. 2007a;22(suppl 1):**S**36. **ASBMR 2009 Annual Meeting. Abstract 1122. doi.org/10.1002/jbmr.5650221402**

Li X, Warmington KS, Niu QT, et al. Treatment with an anti-sclerostin antibody directly stimulates bone formation in a dose-dependent manner in ovariectomized rats with established osteopenia. *J Bone Miner Res*. 2007b;22(suppl 1):**S**65. **ASBMR 2009 Annual Meeting. Abstract 1231. doi.org/10.1002/jbmr.5650221403**

McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women . Hip Intervention Program Study Group. *N Engl J Med*. 2001;344(5):333-340. **doi:10.1056/NEJM200102013440503**

Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001;344(19):1434-1441. **doi:10.1056/NEJM200105103441904**

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001**(6)**;285:785-795. **doi:10.1001/jama.285.6.785**

Ominsky MS, Li CY, Li X, et al. Inhibition of sclerostin by monoclonal antibody enhances bone healing and improves bone density and strength of non-fractured bones. *J Bone Miner Res*. 201**1;26(5)**. doi:10.1002/jbmr.307

Ominsky MS, Niu QT, Kurimoto P, Ke HZ. Tissue level mechanism of increased bone formation by sclerostin antibody in male cynomolgus monkeys. *J Bone Miner Res*. 2010:25(suppl 1):**S**53. **ASBMR 2010 Annual Meeting. Abstract 1174:53. doi.org/10.1002/jbmr.5650251301**

Papapoulos S, Makras P. Selection of antiresorptive or anabolic treatments for postmenopausal osteoporosis. *Nat Clin Pract Endocrinol Metab*. 2008;4(9):514-523. **doi:10.1038/ncpendmet0941**

Park EJ, Joo IW, Jang MJ, et al. Prevalence of osteoporosis in the Korean population based on Korea National Health and Nutrition Examination Survey (KNHANES), 2008-2011. *Yonsei Med J*. 2014;55(4):1049-**10**57. **doi:10.3349/ymj.2014.55.4.1049**

Poole KE, van Bezooijen RL, Loveridge N, et al. Sclerostin is a delayed secreted product of osteocytes that inhibits bone formation. *FASEB J*. 2005;19(13):1842-1844. **doi:10.1096/fj.05-4221fje**

Reginster JY, Burlet N. Osteoporosis: a still increasing prevalence. *Bone*. 2006;38(2 suppl 1):S4-S9. **doi:10.1016/j.bone.2005.11.024**

Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med*. 2017; 377(15):1417-1427. **doi:10.1056/NEJMoa1708322**

Van Bezooijen RL, Roelen BA, Visser A, et al. Sclerostin is an osteocyte-expressed negative regulator of bone formation, but not a classical BMP antagonist. *J Exp Med*. 2004;199(6):805-814. **doi:10.1084/jem.20031454**

Vanhoenacker FM, Balemans W, Tan GJ, et al. Van Buchem disease: lifetime evolution of radioclinical features. *Skeletal Radiol*. 2003;32(12):708-718. **doi:10.1007/s00256-003-0675-4**

Winkler DG, Sutherland MK, Geoghegan JC, et al. Osteocyte control of bone formation via sclerostin, a novel BMP antagonist. *EMBO J*. 2003;22(23):6267-6276. **doi:10.1093/emboj/cdg599**

World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva, Switzerland. 1994:1-129. **https://apps.who.int/iris/handle/10665/39142**

16. Appendices

Appendix A. List of Stand-alone Documents

None

Appendix B. Sample Safety Reporting Form(s)

Observational Research Safety Reporting Form Instructions

This form is for use for observational studies that are using paper report form

General Instructions

The protocol will provide instruction on what types of events to report for the study. *Indicates a mandatory field.

What to report on this form:

- **All adverse events (AEs) are associated with the Amgen drug irrespective of causal relationship of the event to the study drug or seriousness, unless instructed differently by the protocol.**
- **The following safety findings are to be reported on this form as events regardless of association with an AE:**
  - **medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving the Amgen product**
  - **transmission of infectious agents**
  - **reports of uses outside the terms for authorized use of the product including off label use**
  - **occupational exposure**
  - **any lack or loss of intended effect of the product(s)**
  - **product complaint (PC)**
  - **adverse device effect (ADE)**

The following should not be reported on this form and should be reported via the normal process set up for the study

- **pregnancy and lactation reports**

1. **Initial or Follow-up*** – Please tick the appropriate box
2. **Site Number* –** Enter your assigned site number for this study. **Subject Number* –** Enter the entire number assigned to the subject.
3. **Indicate event type* –** Tick the relevant box which applies to the event(s) you are reporting. Please note, more than one box can be ticked.
4. **Contact Details* –** Provide your name, phone, address, etc. (These contact details should be for the Vendor or Investigator)
5. **Reporter ID* –** Provide name or ID of reporter, phone, address, etc. (This could be the Investigator details if vendor details are added in section 4.
6. **HCP Contact Details (if other than reporter)* –** Provide name or ID of reporter, country, phone, address, etc.
7. **Patient* –** Enter the subjects demographic information.
8. **Medical History (include primary diagnosis)* –** 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.
9. **Suspect Product Information (include dosing details)* –** Provide Product/Device information, Indication, start date, stop date, dose, route, frequency, Lot#, Serial#. It is important that all efforts are taken to provide the Lot number, were possible.
10. **AE, Other Safety Finding, PC/ADE Information*:**

AE 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.

Onset Date* – Enter date the AE first started rather than the date of diagnosis or hospitalization. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**

Resolved Date* – Enter date the AE ended. For serious events, this is 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.

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 AE. Protocol specified hospitalizations are exempt.

Serious Criteria Code* – This is a mandatory field for serious events. Select the appropriate code for the event(s) being reported

Action Taken* – State what action has been taken with suspect drug/device.

Outcome* – Enter the code for the outcome of the event at the time the form is completed if outcome is known.

Severity* – State the severity of the safety event being reported.

Reporter Signature: _____ Page 1 of ____

The data provided by you will be transferred as a report to Global Patient Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes

FORM-067756 Ver. #: 4.0 Effective date: 06-Nov-2017

Relationship to Product/Device*:

Relationship to Amgen drug under study* – The Investigator must determine and enter the relationship of the event to the Amgen drug under study at the time the event is initially reported.

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)**

11. **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.

12. **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.

13. **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).

14. **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 each page and fax the form to Amgen.

Reporter Signature: _____ **Page 2 of** ____

The data provided by you will be transferred as a report to Global Patient Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes

FORM-067756 Ver. #: 4.0 Effective date: 06-Nov-2017

Project ID: 20170753	A	**Observational Research Safety Reporting Form**	Date of Reporter Awareness:
			Date Reported to Amgen:
	Fax reports to: Amgen Local Office 080 908 0982		

1. Initial: ☐ Follow-up: ☐

2. Site Number: Subject Number:

3. Indicate event type: *(Please tick all that apply)* ☐ AE/Other Safety Finding ☐ Product Complaint (PC) ☐ Adverse Device Effect (ADE)

4. Contact Details (Vendor/Investigator)

Name	Phone	Fax
Address		
City	State/Province	
Postal Code	Country	

5. Reporter ID

Name or ID	Phone	Fax
Address		
City	State/Province	
Postal Code	Country	

6. HCP Contact Details (if other than reporter)

Name		
Country		
Address		
City	State/Province	Postal Code
Phone	Fax	

7. Patient

Initials (optional)	Sex	Age (at time of event)	Was consent obtained to follow-up with HCP?
	☐ F ☐ M		☐ Yes ☐ No
Weight	Height	Race	Is patient also reporter?
☐ lbs ☐ kg	☐ in ☐ cm		☐ Yes ☐ No

8. Medical History (include primary diagnosis)

9. Suspect Product Information (include dosing details)

Product/Device: _____

Indication: _____

	Start Date (day month year)	Stop Date (day month year)	Dose	Route	Frequency

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial Size

10. AE, Other Safety Finding, or PC/ADE information — **HCP ONLY**

Finding (List main event first; one event per line)	Onset Date (day month year)	Resolved Date (If patient died, list date of death) Cause of Death: (provide autopsy report) (day month year)	Hospitalization: Hospitalized? ☐ Yes ☐ No; Prolonged Hospitalization? ☐ Yes ☐ No; Admitting dx _____; Date Admitted (day month year)	Hospitalization: Date Discharged (day month year)	Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/Prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly/birth defect; 06 Other significant medical hazard; 07 Non serious	Action Taken: 1=none; 2=dose reduced; 3=dose increased; 4=drug withdrawn; 5=drug rechallenge (state outcome)	Outcome: 01 Recovered/ Resolved; 02 Recovering/ Resolving; 03 Not recovered/not resolved; 04 Recovered/ resolved with sequelae; 05 Fatal; 06 Unknown	Severity: 1=mild 2=moderate 3=severe	Relationship to Product/Device: Is there a reasonable possibility that this event may have been caused by the Product/Device? Product	Device
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N

Reporter Signature: _____ Page 3 of ____

The data provided by you will be transferred as a report to Global Patient Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes

FORM-067756 Ver. #: 4.0 Effective date: 06-Nov-2017

11. Concomitant Medications (eg, chemotherapy)

Medication Names	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No	 Yes	Continuing No	 Yes	Dose	Route	Frequency	Treatment Meds

12. Relevant Laboratory Values (include dates, allergies, and any relevant prior therapy)

Date Day Month Year	Test										
	Unit										

13. Other Relevant Test (diagnostics and procedures)

Date Day Month Year	Additional Tests	Results	Units

14. Description: Provide chronological summary and details of AE symptoms, PC or ADE that are listed in section 10 (signs, diagnosis, treatment, concomitant medications including those used to treat event).

Reporter Signature: _____ Page 4 of ____

The data provided by you will be transferred as a report to Global Patient Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes
FORM-067756 Ver. #: 4.0 Effective date: 06-Nov-2017

Appendix C. Additional Safety Reporting Information

Adverse Event Severity Scoring System

The Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, is available at the following location:

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

Appendix D. 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: 20170753

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____(in years)

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

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

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

AMGEN® 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: 20170753

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

Appendix E. Adverse Event, Other Safety Findings, and Product Complaints Report Reconciliation Form

Observational Research Reconciliation Form for Reportable Events

Instructions for Vendor: This form must be completed by providing a summary/listing of all Reportable Events previously submitted to Amgen **every quarter of the year** unless a different reconciliation period was agreed per contractual agreement. A "Reportable Event" is an Adverse Event (AE), Other Safety Finding (OSF), or a Product Complaint (PC). In addition, a final listing of all Reportable Events must be sent to Amgen at the end of study. Indicate in the fields below if this listing is Periodic or Final, as well as providing the reconciliation dates covered. A Vendor's own form/listing can be used provided all data fields on this form are also contained in the Vendor's own form/listing. The shaded area of this form must always be completed and attached as a coversheet to the Vendor's own form/listing of events.
Email completed forms to: CSL-Reconciliation@amgen.com (Please always copy the Amgen Study Manager when submitting Observational Research reconciliation forms to this email address).

AMGEN	Protocol Title:	
	Protocol/Study Number:	
	Vendor Name:	
Date of Reconciliation Form submitted to Amgen:		Additional Information/Comments:
Vendor contact information for this report:		
• Name:		Reconciliation Type: Periodic ☐ OR Final ☐
• Telephone Number:		Reconciliation Period Start Date:
• Email Address:		Reconciliation Period Stop Date:

The following is a summary of individual Adverse Events, Other Safety Findings and Product Complaints previously reported to the Company's Drug Safety Department. If the number of events exceeds the number of rows on this form, please use an additional form.

Country of Occurrence	Subject ID	Site #	Amgen Product	Preferred Term OR Product Complaint Term	Severity	Relationship to Investigational product (*Amgen product under study*)	Serious (Y/N)	Date of Onset

☐ **No individual Adverse Events / Other Safety Findings / Product Complaints were identified and submitted to Amgen during the defined reconciliation period as listed above.**

Appendix F. ENCePP Checklist for Study Protocols

Amgen Proprietary - Confidential

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Postmarketing Surveillance Study of EVENITY (Romosozumab) in South Korea

EU PAS Register® number: EUPAS30346
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6.
1.1.2 End of data collection[2]	☒	☐	☐	6.
1.1.3 Progress report(s)	☒	☐	☐	6.
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☐	☐	6.
1.1.6 Final report of study results.	☒	☐	☐	6.

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

1.1.4: MFDS don't require interim report for mandatory PMS. Therefore, we don't have specific timeline for interim report.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7.2,7.3,8,9.2.3
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8.1,8.2,8.3
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.3
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	7.3
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	7.3

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.1
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9.1

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.3
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.1
4.2.2 Age and sex	☒	☐	☐	9.2.3.1
4.2.3 Country of origin	☒	☐	☐	9.2.3.1
4.2.4 Disease/indication	☒	☐	☐	9.2.3.1
4.2.5 Duration of follow-up	☒	☐	☐	9.2.1

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.1
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Patients will be given study drug per local label since this is a observational, single-arm, postmarketing study.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9.1.4
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9.1.2

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.2.5.1

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☒	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☐	☒	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	
9.3.3 Covariates and other characteristics?	☐	☐	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	9.6.2

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.2.1
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2.3.1
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.9.1.4
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.9.1.1
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.9.3
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.2.5

Comments:

The statistical analysis in this PMS study will be descriptive in nature, and no hypothesis testing will be performed.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.3.2
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6.3
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.6.3

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	9.9.1.3
12.1.2 Information bias?	☒	☐	☐	9.9.1.2
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9.1.4
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.9.3

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.2
13.3 Have data protection requirements been described?	☒	☐	☐	10.3

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	12.1

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	13
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13.1

Comments:

Name of the main author of the protocol: PPD

Date: 14/Sep/2021

Signature: PPD

ENCePP Checklist for Study Protocols (Revision 4) Page 6/6