Summary Report of Benefit-Risk Assessment

EVENITY SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE 105 MG/1.17 ML

NEW DRUG APPLICATION

Active Ingredient(s)	Romosozumab
Product Registrant	Amgen Biotechnology Singapore Pte Ltd
Product Registration Number	SIN16208P
Application Route	Abridged evaluation
Date of Approval	27 May 2021

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A INTRODUCTION

Evenity is indicated for the treatment of severe osteoporosis in post-menopausal women at high risk of fracture.

The active substance, romosozumab, is a humanised immunoglobulin G2 monoclonal antibody and is a first-in-class sclerostin inhibitor. Inhibition of sclerostin leads to a transient stimulation of bone formation and inhibition of bone resorption. This dual effect of increasing bone formation and decreasing bone resorption results in rapid increases in trabecular and cortical bone mass and improvements in bone structure and strength.

Evenity is available as a solution for subcutaneous injection in a pre-filled syringe containing romosozumab 105mg in 1.17mL solution. It is a sterile, preservative-free, clear to opalescent, colourless to light yellow solution at pH 5.2.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, romosozumab, is manufactured at Immunex Rhode Island Corporation, Rhode Island, USA. The drug product, Evenity, is manufactured at Patheon Italia S.p.A., Monza, Italy and packaged at Amgen Manufacturing Limited, Puerto Rico, USA.

Drug substance:

Adequate controls have been presented for the raw materials, reagents, cell substrate and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Product-related and process-related impurities are adequately controlled.

The drug substance specifications were established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used were adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and purity testing was presented.

The stability data presented for Immunex Rhode Island Corporation, Rhode Island, USA were adequate to support the approved storage condition and shelf life. The drug substance is packed in 10 L polycarbonate carboy containers sealed with a polypropylene screw cap closure containing a thermoplastic elastomer gasket. The drug substance is approved for storage at or below -30°C with a shelf life of 60 months.

Drug product:

The manufacturing process utilises aseptic processing which is considered to be a standard process.

All manufacturing sites involved are compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used were adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data submitted were adequate to support the approved shelf-life of 36 months when stored between 2 and 8ºC. There is a provision for an optional short-term storage at temperatures below 25°C for up to 30 days which is supported with appropriate data. The product should be stored protected from light. The container closure system is a 1 mL syringe with a 27 G stainless steel needle covered with an elastomeric needle shield and a chlorobutyl elastomeric plunger-stopper. Two pre-filled syringes are supplied in each carton.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy data to support the use of romosozumab in the treatment of osteoporosis in postmenopausal women (PMO) at high risk of fracture was supported by two pivotal Phase III, randomised, double-blind studies, ARCH and FRAME and one supportive study STRUCTURE.

Pivotal Alendronate-controlled study (Study 20110142; ARCH)

Study ARCH was a Phase III, double-blind, randomised, event-driven study evaluating romosozumab compared to alendronate in post-menopausal women with osteoporosis (PMO) and previous fragility fractures.

Subjects in the study were randomised in a 1:1 ratio to receive either romosozumab 210 mg via two subcutaneous injections once monthly or oral alendronate 70 mg once weekly for the first 12 months in the double-blind phase; following which romosozumab was stopped and all subjects received open-label alendronate in the second year. All subjects received daily calcium (500 to 1000 mg) and vitamin D (600 to 800 IU) supplementation. The use of alendronate as an active comparator was considered acceptable. Spine X rays were obtained at screening, Months 6, 12 and 24. Vertebral fractures were determined using X rays, CT or MRI. A medical report was acceptable if imaging reports were not available.

The primary efficacy endpoints were i) the incidence of new vertebral fractures at Month 24 and ii) the incidence of clinical fracture (non-vertebral fracture or clinical vertebral fracture) at the primary analysis. The primary analysis was performed when all women had completed the Month 24 study visit and clinical fracture events were confirmed for at least 330 women, which occurred after a median of 33 months on study. The key secondary endpoints were the percent change from baseline in bone mineral density (BMD) at lumbar spine, total hip and femoral neck at Months 12 and 24, and the incidence of non-vertebral fractures at primary analysis. A fixed-sequence testing procedure was used for multiplicity adjustment of the two primary and key secondary efficacy endpoints to maintain the overall significance level at 0.05.

A total of 4,093 PMO subjects aged 55 to 90 years old with previous fragility fractures were studied. The patient demographics and baseline disease characteristics were generally balanced between the treatment arms. The mean age of the study population was 74 years old and 7.0% were Asian. Overall, 96.1% of women had a vertebral fracture at baseline, and 99.8% of women had a previous fracture. The mean baseline lumbar spine, total hip and femoral neck BMD T-scores were −2.96, −2.80 and −2.90, respectively.

Treatment with romosozumab resulted in a significant decrease in fractures compared to alendronate treatment. The incidence of new vertebral fractures at Month 24 was 4.1% (74/1825) in the romosozumab group compared to 8.0% (147/1834) in the alendronate group with an absolute risk reduction of 4.03% (95% CI: 2.50%, 5.57%) and a relative risk reduction of 50% (95% CI: 34%, 62%; p<0.001). Through the primary analysis period, the incidence of clinical fracture was 9.7% (198/2046) in the romosozumab group and 13.0% (266/2047) in the alendronate group, with a relative risk reduction of 27% (95% CI: 12%, 39%; p<0.001). The results were statistically significant.

The increase in BMD from baseline was consistently higher in the romosozumab group than in the alendronate group at Month 12 at the lumbar spine (13.7% vs 5.0%), total hip (6.2% vs 2.8%) and femoral neck (4.9% vs 1.7%); statistical significance (p<0.001) was reached at all locations. At Month 24, romosozumab for 12 months followed by alendronate for 12 months significantly increased BMD from baseline compared to alendronate alone for 24 months at the lumbar spine (15.3% vs 7.2%), total hip (7.2% vs 3.5%) and femoral neck (6.0% vs 2.3%); statistical significance (p<0.001) was also reached at all locations.

Romosozumab also significantly reduced the risk of nonvertebral fractures compared to alendronate. Through the primary analysis period, the incidence of nonvertebral fracture was 8.7% (178/2046) in the romosozumab group and 10.6% (217/2047) in the alendronate group, yielding a relative risk reduction of 19% (95% CI: 1%, 34%; p=0.040).

The study was not powered to assess the effect of romosozumab on hip fractures, but a favourable point estimate was observed compared to alendronate at both Month 12 (relative risk reduction 36% [95% CI: -26%, 67%]) and at the time of primary analysis (relative risk reduction 38% [95% CI: 8%, 58%]).

Summary of Key Efficacy Endpoints (Study 20110142)*

	Alendronate/ Alendronate	**Romosozumab/ Alendronate**	**Relative Risk Reduction (95% CI)**	**P value**
Primary endpoints				
Vertebral fracture, Month 24 (%)	8.0	4.1	50 (34, 62)	<0.001
Clinical fracture, primary analysis (%)	13.0	9.7	27 (12, 39)	<0.001
	Alendronate/ Alendronate	**Romosozumab/ Alendronate**	**LS mean difference (95% CI)**	**P value**
Key secondary endpoints (percent change from baseline in BMD)				
BMD (lumbar spine), Month 24, LS mean CFB (%)	7.2	15.3	8.1 (7.58, 8.57)	<0.001
BMD (total hip), Month 24, LS mean CFB (%)	3.5	7.2	3.8 (3.42, 4.10)	<0.001
BMD (femoral neck), Month 24, LS mean CFB (%)	2.3	6.0	3.8 (3.40, 4.14)	<0.001

BMD (lumbar spine), Month 12, LS mean CFB (%)	5.0	13.7	8.7 (8.31, 9.09)	<0.001
BMD (total hip), Month 12, LS mean CFB (%)	2.8	6.2	3.3 (3.03, 3.60)	<0.001
BMD (femoral neck), Month 12, LS mean CFB (%)	1.7	4.9	3.2 (2.90, 3.54)	<0.001
	Alendronate/ Alendronate	**Romosozumab/ Alendronate**	**Relative Risk Reduction (95% CI)**	**P value**
Key secondary endpoints (fractures)				
Non-vertebral fracture, primary analysis (%)	10.6	8.7	19 (1, 34)	0.040

*presented in the sequence of hierarchical testing
CFB: change from baseline

Pivotal placebo-controlled study (Study 20070337; FRAME)

Study FRAME was a Phase III, 24-month, multicentre, double-blind, randomised, placebo-controlled study evaluating romosozumab in PMO subjects. In the first 12 months, subjects received either subcutaneous romosozumab 210 mg monthly or placebo. All subjects were switched to open-label subcutaneous denosumab 60 mg every 6 months in the second year. All subjects received daily calcium (500 to 1000 mg) and vitamin D (600 to 800 IU) supplementation. Spine X rays were obtained at screening, Month 6, 12 and 24. Non-vertebral fractures were confirmed using X rays, CT or MRI. A medical report was acceptable if imaging reports were not available.

The co-primary endpoints were the incidence of new vertebral fractures at Month 12 and Month 24. The key secondary endpoints included clinical fractures at Month 12 (defined as non-vertebral fractures and symptomatic vertebral fractures), non-vertebral fractures at Months 12 and 24 and hip fractures at Months 12 and 24. A fixed-sequence testing procedure was used for multiplicity adjustment of the co-primary and key secondary efficacy endpoints to maintain the overall significance level at 0.05.

A total of 7,180 PMO subjects were randomised to study treatment. The patient demographics and baseline disease characteristics were generally balanced between the treatment arms. The mean age of the studied population was 71 years old and 12.1% were Asian. Baseline mean BMD T-scores were -2.72 at lumbar spine and -2.47 at total hip and -2.75 at femoral neck. This study recruited a population of less severe PMO subjects compared to study 20110142 (ARCH), as subjects with BMD T-score of ≤-3.5 at the total hip or femoral neck, history of hip fracture, severe vertebral fracture or more than 2 moderate vertebral fractures were excluded. A total of 18.7% of patients in the romosozumab group and 18.0% in the placebo group had a prevalent vertebral fracture at baseline, as evaluated by the central imaging vendor.

Treatment with romosozumab resulted in a significant decrease in new vertebral fractures compared to placebo at Month 12. The incidence of new vertebral fractures at Month 12 was 0.5% (16/3321) in the romosozumab group compared to 1.8% (59/3322) in the placebo group, with an absolute risk reduction of 1.30% (95% CI: 0.79%, 1.80%) and a relative risk reduction of 73% (95% CI: 53%, 84%). At Month 24, patients who were initially randomised to romosozumab had significantly fewer vertebral fractures than placebo after all subjects switched to denosumab. The incidence of new vertebral fractures was 0.6% (21/3325) in the romosozumab/denosumab group compared to 2.5% (84/3327) in the placebo/denosumab

group, with an absolute risk reduction of 1.89% (95% CI: 1.30%, 2.49%) and a relative risk reduction of 75% (95% CI: 60%, 84%).

Romosozumab significantly reduced the risk of clinical fractures (nonvertebral and clinical vertebral fractures) by 36% (95% CI: 11%, 54%) compared to placebo through Month 12 (p = 0.008). However, the reduction in non-vertebral fractures at Month 12 was not significant (p=0.096), although a clear separation between treatment groups in favour of romosozumab was observed. The remaining endpoints in the testing sequence were not formally tested for statistical significance. Nevertheless, favourable point estimates were noted compared to placebo at both Month 12 and Month 24.

Summary of Key Efficacy Endpoints (Study 20070337)*

	Placebo/ Denosumab	Romosozumab/ Denosumab	Absolute Risk Reduction (95% CI)	Relative Risk Reduction (95% CI)	P value
Primary endpoints					
Vertebral fracture, Month 12 (%)	1.8	0.5	1.30 (0.79, 1.80)	73 (53, 84)	<0.001
Vertebral fracture, Month 24 (%)	2.5	0.6	1.89 (1.30, 2.49)	75 (60, 84)	<0.001
Key secondary endpoints					
Clinical Fracture, Month 12 (%)	2.5	1.6	1.2 (0.4, 1.9)	36 (11, 54)	0.008
Nonvertebral Fracture, Month 12 (%)	2.1	1.6	0.8 (0.1, 1.4)	25 (-5, 47)	*0.096*
Nonvertebral Fracture, Month 24 (%)	3.6	2.7	1.0 (0.2, 1.9)	25 (3, 43)	Testing stopped
Clinical Fracture, Month 24 (%)	4.1	2.8	1.4 (0.5, 2.4)	33 (13, 48)	-
Hip Fracture, Month 12 (%)	0.4	0.2	0.9 (0.0, 0.6)	46 (-35, 78)	-
Hip Fracture, Month 24 (%)	0.6	0.3	0.4 (0.0, 0.7)	50 (-4, 76)	-

*presented in the sequence of hierarchical testing

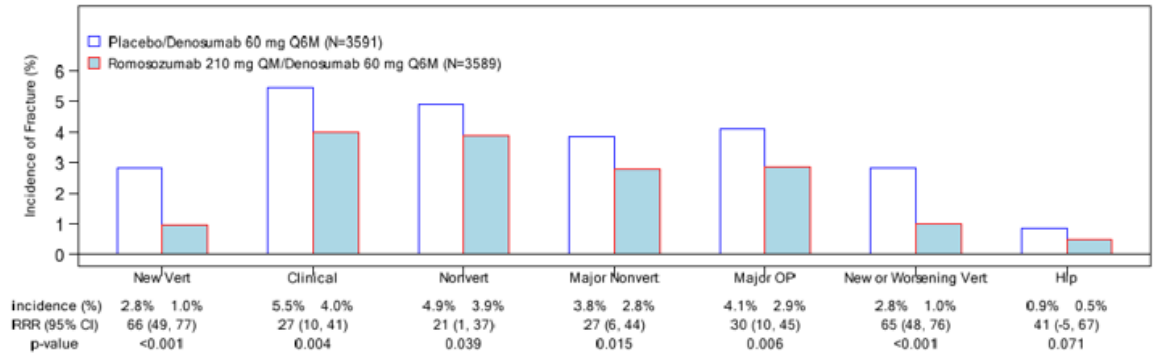
A consistent treatment effect favouring romosozumab over placebo was generally observed in the subgroups explored including age and presence/absence of prevalent vertebral fracture.

The increase in BMD from baseline was markedly higher in the romosozumab group than in the placebo group at Month 12 at the lumbar spine (13.1% vs 0.4%), total hip (6.0% vs 0.3%) and femoral neck (5.5% vs 0.3%); statistical significance (p<0.001) was reached at all locations. At Month 24, romosozumab followed by denosumab maintained the increases in BMD at the lumbar spine (16.6% vs 5.5%), total hip (8.5% vs 3.2%) and femoral neck (7.3% vs 2.3%); statistical significance (p<0.001) was also reached at all locations.

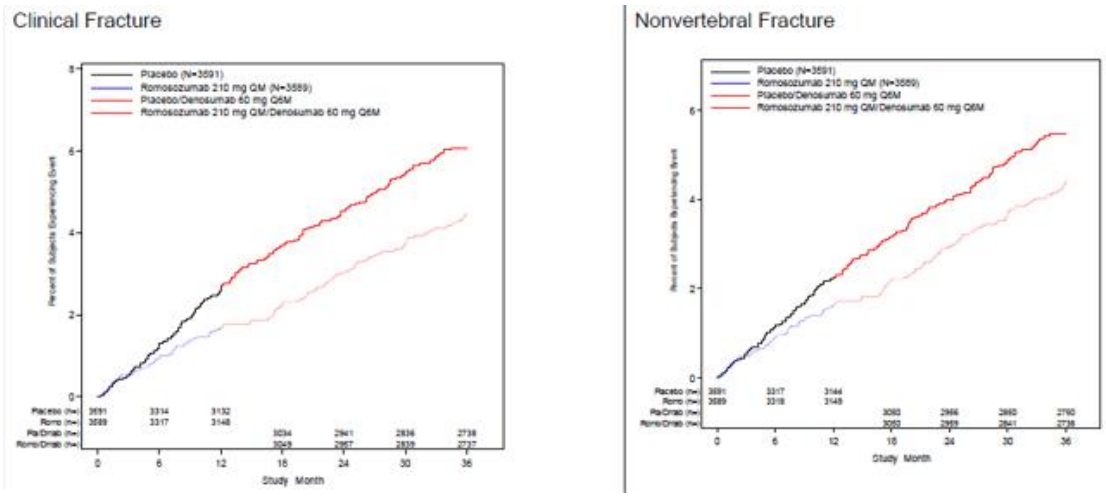
Extension phase through Month 36

A lower fracture risk was observed through Month 36 for new vertebral, clinical, non-vertebral, major non-vertebral, major osteoporotic and new or worsening vertebral fractures in the romosozumab group compared to the placebo group, despite both treatment groups having switched to denosumab after the first 12 months of double-blind treatment.

Incidence of key fracture endpoints through Month 36 (Study 20070337)



Cumulative incidence of clinical fracture and non-vertebral fracture through Month 36 (Study 20070337)



Women transitioning from bisphosphonate therapy

The supportive study STRUCTURE (20080289) was a Phase IIIb, multicentre, randomised, open-label study comparing romosozumab to teriparatide in PMO subjects with severe osteoporosis transitioning from bisphosphonate use. The study population had a high risk for fracture, defined as low BMD at lumbar spine, total hip or femoral neck, and with evidence of a previous fracture. Subjects were randomised to receive either subcutaneous romosozumab 210 mg once a month or subcutaneous teriparatide 20 ug once daily for 12 months. All subjects received daily calcium (500 to 1000 mg) and vitamin D (600 to 800 IU) supplementation.

The primary efficacy variable was the percent change in total hip BMD from baseline at Month 12. The study was not designed to assess for fracture data.

A total of 436 subjects were randomised to study treatment. The patient demographics and baseline disease characteristics were generally balanced between the treatment arms. The mean age was 71.5 years (range: 56-90 years) and only 0.5% were Asian. Enrolled women had a mean baseline lumbar spine, total hip and femoral neck BMD T-scores of –2.85, −2.24, and –2.46, respectively, and a history of nonvertebral fracture after age 50 or vertebral fracture at any time. All subjects received oral bisphosphonate therapy in the 3 years immediately prior to screening. The majority of subjects received prior alendronate (92.7% in teriparatide group and 88.1% in romosozumab group) during this period.

Romosozumab significantly increased BMD at the total hip relative to teriparatide at Month 12 (2.9% vs -0.5%; mean treatment difference from teriparatide: 3.4% [95% CI: 2.8%; 4.0%]; p<0.0001). In addition, treatment difference in BMD at 12 months compared to teriparatide were 4.4% (9.8% vs 5.4%; [95% CI: 3.4%, 5.4%]; p<0.0001) at the lumbar spine and 3.4% (3.2% vs -0.2%; [95% CI 2.6, 4.2]; p<0.0001) at the femoral neck.

Overall, the clinical efficacy of romosozumab in the treatment of osteoporosis in post-menopausal women was demonstrated.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of romosozumab in postmenopausal women with osteoporosis was mainly derived from the 12-month romosozumab treatment periods in studies ARCH and FRAME, comprising 5,621 patients.

Overview of Safety Profile (12-month PMO Fracture Trial Safety Analysis Set)

AE	Control (N=5590)	Romosozumab (N=5621)
Any AE	4447 (79.6%)	4355 (77.5%)
Treatment-related AE	808 (14.5%)	896 (15.9%)
Serious adverse events (SAE)	592 (10.6%)	606 (10.8%)
Treatment-related SAE	25 (0.4%)	29 (0.5%)
Study discontinuations due to AE	77 (1.4%)	73 (1.3%)
Deaths due to AE	46 (0.8%)	59 (1.0%)

AE: adverse event; SAE: serious adverse event

A total of 77.5% of subjects in the romosozumab group and 79.6% in the control group reported at least one adverse event (AE). Treatment-related AEs were reported at similar incidence rates of 15.9% in the romosozumab group vs 14.5% in the control group. Most of these events were mild to moderate in severity. The most common AEs and their incidences (romosozumab vs control) were viral upper respiratory tract infection (14.1% vs 14.5%), arthralgia (11.3% vs 11.2%) and back pain (10.0% vs 10.9%). Most of these events were mild to moderate in severity. Treatment-related AEs reported in romosozumab group included arthralgia (2.0% vs 1.7%), pain in extremity (1.6% vs 1.1%), myalgia (1.3% vs 1.0%) and injection site pain (1.2% vs 0.9%).

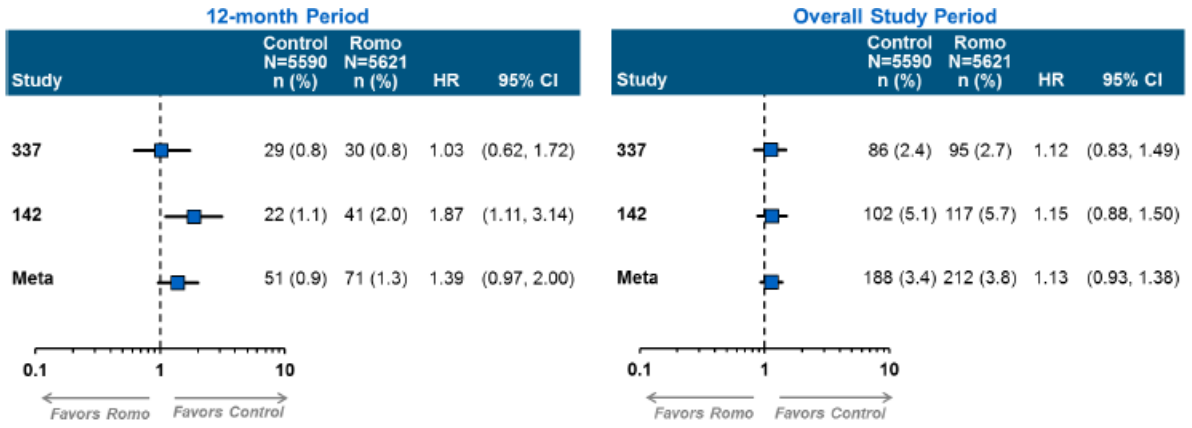
The incidence of serious adverse events (SAEs) was similar between romosozumab and control groups (10.8% and 10.6%, respectively). Pneumonia (0.6% vs 0.5%) was the most frequently reported SAE, followed by femur fracture (0.3% vs 0.3%). None of the femur fractures were positively adjudicated as atypical femoral fractures. Treatment-related SAEs were reported in ~1% of subjects, and there was no clustering of SAEs in any System Organ Class.

AEs of special interest include hypocalcaemia (n=2 in romosozumab versus n=1 in control), hypersensitivity (n=364 [6.5%] in romosozumab versus n=365 [6.5%] in control), injection site reactions (n=278 [4.9%] in romosozumab versus n=157 [2.8%] in control), atypical femoral fracture (n=1 in romosozumab) and osteonecrosis of the jaw (n=1 in romosozumab), which were identified/potential risks of romosozumab. These identified risks were described as warnings in the approved product labelling.

Major adverse cardiovascular events (MACE)

The most significant safety signal for romosozumab was the imbalance in adjudicated MACE events (defined as a composite of myocardial infarction [MI], stroke and death) observed in study ARCH during the first 12 months of treatment, but not observed in the FRAME study nor in the overall study period. In terms of baseline characteristics, the study populations were generally balanced between the treatment groups within each study, including CV-related medical history.

Time to first adjudicated MACE through Month 12 and the overall study period (Safety Analysis Set, Studies 20070337 and 20110142)



HR = hazard ratio; Meta = meta-analysis; Romo = romosozumab

The number of subjects with MACE events during the 12-month double-blind romosozumab treatment phase in the ARCH study was 41 (2.0%) in the romosozumab group versus 22 (1.1%) in the alendronate group, yielding a hazard ratio (HR) of 1.87 (95% CI 1.11, 3.14) for romosozumab compared to alendronate. In addition, 16 subjects (0.8%) had MI in the romosozumab arm versus 5 subjects (0.2%) in the alendronate arm and 13 subjects (0.6%) had stroke in the romosozumab arm versus 7 subjects (0.3%) in the alendronate arm. These events occurred in patients with or without a history of MI or stroke. Cardiovascular (CV) death occurred in 17 subjects (0.8%) in the romosozumab group and 12 (0.6%) subjects in the alendronate group. All-cause death occurred in 30 subjects (1.5%) in the romosozumab group and 22 (1.1%) subjects in the alendronate group. In subgroup analyses by baseline characteristics and history of cerebrovascular events and/or cardiac ischemic events, the increased risk of MACE events through Month 12 was consistently elevated on romosozumab compared to alendronate or placebo in all subgroups. Nonetheless, the imbalance in MACE events between treatment groups was no longer evident (HR 1.15 [0.88, 1.50]) when the subjects were followed through till the end of the study period, with a median follow-up time of approximately 33 months.

During the 12-month double-blind romosozumab treatment phase in the placebo-controlled FRAME study, there was no difference in positively adjudicated MACE; 30 (0.8%) occurred in the romosozumab group and 29 (0.8%) in the placebo group. All-cause death occurred in 29 subjects (0.8%) in the romosozumab group and 24 (0.7%) subjects in the placebo group.

In the supportive STRUCTURE study in women with PMO, cardiovascular events were not adjudicated. A numerical imbalance in AEs of cardiac disorders (5.0% vs 3.7%) and vascular disorders (7.3% vs 3.3%) were observed. In addition, serious cardiac disorders were reported

in 2.3% for romosozumab and 0.9% for teriparatide. One serious cerebrovascular accident, one ischaemic stroke and one transient ischaemic attack were reported in the romosozumab group vs none in the teriparatide group.

Deaths

All fatal AEs in these studies were adjudicated and categorised as CV or non-CV-related deaths. Deaths which could not be confirmed to be CV-related were assumed to be CV in the analysis.

In the ARCH study, 22 subjects (1.1%) in the alendronate group versus 30 romosozumab subjects (1.5%) had a fatal AE whereas in the FRAME study, 24 placebo subjects (0.7%) versus 29 romosozumab subjects (0.8%) had a fatal AE.

The incidence of non-CV deaths in the 12-month double-blind period was generally balanced in both studies, with the majority of deaths in both studies being due to malignancies (22 of 43 cases).

CV mortality ("CV death" + "Undetermined") was generally balanced in the FRAME study (17 romosozumab-treated subjects (0.5%) and 15 placebo-treated subjects (0.4%) had adjudicated CV deaths). In the ARCH study, a numerical imbalance in the incidence of CV deaths was observed, comprising 17 romosozumab subjects (0.8%) compared to 12 alendronate subjects (0.6%). Of these, 5 romosozumab subjects compared to 2 alendronate subjects had fatal MIs or strokes. The incidence of non-MI or non-stroke fatal CV events was balanced (9 events in romosozumab group and 8 events in alendronate group).

When analysed by age, an imbalance in death in subjects ≥75 years old was observed with higher number of events associated with romosozumab treatment compared to placebo or the active control during the 12-month double-blind period in both studies ARCH and FRAME, see table below.

The relatively small number of events (n=105; <1%) limits the ability to draw definitive conclusions, particularly when these numbers become even smaller when split by age groups; and that these events may be confounded by existing medical comorbidities in this frail population.

Subject incidence of fatal adjudicated AEs in the 12-month double-blind period in 20070337 (FRAME) and 20110142 (ARCH)

Study	20070337		20110142	
Treatment	Placebo n/N (%)	Romosozumab n/N (%)	ALN n/N (%)	Romosozumab n/N (%)
Overall	24/3576 (0.7)	29/3581 (0.8)	22/2014 (1.1)	30/2040 (1.5)[a]
<75 years	16/2461 (0.7)	10/2464 (0.4)	5/965 (0.5)	5/970 (0.5)
≥75 years	8/1115 (0.7)	19/1117 (1.7)	17/1049 (1.6)	25/1070 (2.3)[a]
CV Death	8	13	8	14
CV Death	6	5	5	8
Undetermined	2	8	3	6
Non-CV Death	0	6	9	10
Malignancies	0	4	3	5
Other	0	2	6	5

Non-clinical studies have not identified a mechanism by which romosozumab may have contributed to the increased CV events in ARCH study. A literature review on background rates of MACE events revealed a similar range of MACE events in the target patient population. Based on the known mechanism of action, there was no association between sclerostin and/or romosozumab and the key pathological mechanisms underlying MI and stroke, i.e., plaque rupture, plaque erosion, increased thrombogenesis or vasospasm. There is also no genetic evidence for any association between sclerostin and CV risk.

Osteoporosis and CV disease have overlapping risk factors and are associated conditions in epidemiological studies. In the clinical studies, the number of CV events was considered small over the time period examined (22 events [1.1%] in alendronate group [n=2014] vs 41 events [2.0%] in romosozumab group [n=2040] over 12 months in the ARCH study), and the associated hazard ratios may be difficult to interpret given the small number of events. Nevertheless, the potential CV safety signal could not be entirely ruled out. In an exploratory analysis, it was observed that when patients with a history of MI or stroke were excluded from the event rates calculation, the excess MACE events per 1000 patients in the romosozumab versus control group decreased from 23 to 3. This data suggests that restricting the treatment population to a targeted subset by excluding patients with a prior history of MI or stroke may minimise the possible increased CV risk from romosozumab treatment.

Overall, romosozumab presented an acceptable safety profile for the target patient population. Appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Osteoporosis is a disease characterised by low bone mass, disruption of the bone structure and skeletal fragility, resulting in decreased bone strength and an increased risk of fracture. In the context of severe osteoporosis, clinical practice guidelines recommend the use of an anabolic agent as initial treatment in patients with very high risk of fracture (including those with a recent fracture in the last 2 years, multiple prevalent fractures, very low BMD T-scores, very high FRAX [Fracture Risk Assessment Tool] major osteoporotic and/or hip fracture scores). Teriparatide is currently the only anabolic agent available in Singapore, but patient compliance is impacted by the need for daily injections. Hence, there is a medical need for alternative therapies for patients with a higher risk of fractures.

The clinical efficacy of romosozumab in the treatment of osteoporosis in post-menopausal women was demonstrated in studies ARCH and FRAME. Romosozumab produced clinically meaningful and statistically significant reductions in new vertebral fractures (at Month 24) and clinical fractures (at a median follow-up duration of 33 months at time of primary analysis) compared to alendronate in study ARCH. In the placebo-controlled FRAME study, patients who received an initial 1-year treatment with romosozumab experienced significant reductions in new vertebral fracture risk compared to placebo. This benefit persisted after the patients transitioned to denosumab at Month 12 through Month 24, compared to subjects who transitioned from placebo to denosumab. The lowered fracture risk in the romosozumab treatment group was observed through the extension phase to Month 36. Although both studies were not designed to adequately assess effects on hip fracture, there were favourable point estimates for the romosozumab group compared to controls.

In both studies, romosozumab increased BMD at the lumbar spine, total hip, and femoral neck compared to control through Month 24. Furthermore, romosozumab has shown superiority to

teriparatide for rapid increases in BMD from baseline in post-menopausal women with severe osteoporosis transiting from at least 3 years of bisphosphonates therapy in the STRUCTURE study.

The main studies providing safety data for romosozumab in post-menopausal women with osteoporosis were the two large pivotal studies, ARCH and FRAME. AEs were mostly mild to moderate in severity and mainly included viral upper respiratory tract infection, arthralgia, back pain, hypersensitivity reactions, injection site reactions and headache. The most notable safety concerns were MACE, hypocalcaemia, hypersensitivity reactions, osteonecrosis of the jaw and atypical femoral fractures, which have been adequately addressed in the package insert. There were uncertainties with respect to the divergence in CV safety data from the two pivotal fracture studies in PMO women. No plausible mechanism by which romosozumab would impact the risk of MI and stroke has been identified, and no specific subgroups of patients were identified from the clinical data as being at relatively higher risk of MACE.

In view of these uncertainties, the use of romosozumab is recommended only in a restricted population of post-menopausal women at high risk of fracture who require rapid build-up in bone mass was considered favourable, taking into consideration the advantage of rapidly increasing bone mass and quick onset of efficacy.

Risk mitigation measures have been included in the package insert to manage the risk of MACE, including contraindicating its use in patients with a history of MI or stroke, assessing fracture risk and CV risk over the next 12 months by the prescriber and discontinuing romosozumab if a patient experiences a MI or stroke during treatment. The requirements for submission of periodic benefit-risk evaluation reports, as well as results from the observational non-interventional study comparing the clinical characteristics of patients treated with romosozumab versus other approved osteoporotic therapies, were attached as registration conditions to further monitor and confirm the benefit-risk of romosozumab in the approved patient population.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Evenity for the treatment of severe osteoporosis in post-menopausal women at high risk of fracture, with a corresponding contraindication in patients with history of myocardial infarction or stroke, was deemed favourable and approval of the product registration was granted on 27 May 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

EVENITY® solution for injection in pre-filled syringe 105 mg/1.17 mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EVENITY solution for injection in pre-filled syringe 105 mg
Each pre-filled syringe contains 105 mg romosozumab in 1.17 mL (90 mg/mL) solution.

EVENITY (romosozumab) is a humanised monoclonal antibody (IgG2) with high affinity and specificity for sclerostin. Romosozumab has an approximate molecular weight of 145 kDa and is produced in a mammalian cell line (Chinese hamster ovary) by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for subcutaneous injection.

EVENITY is a sterile, preservative-free, clear to opalescent, colourless to light yellow solution, pH 5.2.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Postmenopausal Osteoporosis

EVENITY is indicated for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture.

4.2 Dosage and Administration

Dosage

The recommended dose of EVENITY is 210 mg administered subcutaneously. Administer EVENITY once every month for 12 doses.

Patients should be adequately supplemented with calcium and vitamin D [see Contraindications (4.3), Special Warnings and Precautions for Use (4.4), and Clinical Data (5.1)].

If the EVENITY dose is missed, administer as soon as it can be rescheduled. Thereafter, EVENITY can be scheduled every month from the date of the last dose.

After completing EVENITY therapy, consider transition to another osteoporosis therapy [see Pharmacodynamic Properties 5.1) and Clinical Data (5.1)].

Method of Administration

Subcutaneous use. Administration should be performed by an individual who has been trained to administer the product.

To administer the 210 mg dose, give 2 subcutaneous injections of EVENITY.

For detailed instructions on storage, handling, and administration, follow the directions provided in the "Instructions for Use."

Important Administration Instructions

- Visually inspect EVENITY for particles and discoloration prior to administration. EVENITY is a clear to opalescent, colourless to light yellow solution. Do not use if the solution is cloudy or discoloured or contains particles.

- Administer EVENITY in the abdomen, thigh, or upper arm subcutaneously. If you want to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection. Do not inject into areas where the skin is tender, bruised, red, or hard.

4.3 Contraindications

Hypocalcaemia

EVENITY is contraindicated in patients with uncorrected hypocalcaemia [see Special Warnings and Precautions for Use (4.4), Adverse Reactions (4.8), and Special Populations (4.6)].

Hypersensitivity

EVENITY is contraindicated in patients with known clinically significant hypersensitivity to romosozumab or to any component of the product formulation [see Special Warnings and Precautions for Use (4.4) and List of Excipients (6.1)].

Myocardial Infarction and Stroke

EVENITY is contraindicated in patients with a history of myocardial infarction or stroke [see Special Warnings and Precautions for Use (4.4)].

4.4 Special Warnings and Precautions for Use

Myocardial Infarction and Stroke

In a randomised controlled trial in postmenopausal women, there was a higher rate of major adverse cardiac events (MACE), a composite endpoint of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, in patients treated with EVENITY compared to those treated with alendronate.

Romosozumab is contraindicated in patients with previous myocardial infarction or stroke [see Contraindications (4.3)].

When determining whether to use romosozumab for an individual patient, consideration should be given to her fracture risk over the next year and her cardiovascular risk based on risk factors (e.g. established cardiovascular disease, hypertension, hyperlipidaemia, diabetes mellitus, smoking, severe renal impairment, age). Romosozumab should only be used if the prescriber and patient agree that the benefit outweighs the risk. If a patient experiences a myocardial infarction or stroke during therapy, treatment with romosozumab should be discontinued.

Hypocalcaemia

Transient hypocalcaemia has been observed in patients receiving EVENITY. Correct hypocalcaemia prior to initiating therapy with EVENITY [see Contraindications (4.3), Adverse Reactions (4.8), and Special Populations (4.6)].

Monitor patients for signs and symptoms of hypocalcaemia. Patients should be adequately supplemented with calcium and vitamin D [see Pharmacodynamic Properties (5.1)].

Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m^2) or receiving dialysis are at greater risk of developing hypocalcaemia and the safety data for these patients is limited. Calcium levels should be monitored in these patients.

Hypersensitivity

Clinically significant hypersensitivity reactions, including angio-oedema, erythema multiforme, and urticaria occurred in the EVENITY group in clinical trials. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue further use of EVENITY [see Contraindications (4.3) and Adverse Reactions (4.8)].

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing and has occurred rarely in patients receiving EVENITY in the clinical trials.

Patients who are suspected of having or who develop ONJ while on EVENITY should receive care by a dentist or an oral surgeon. Discontinuation of EVENITY therapy should be considered based on individual benefit-risk assessment.

The following risk factors should be considered when evaluating a patient's risk of developing ONJ:

- potency of the medicinal product that inhibits bone resorption (the risk increases with the antiresorptive potency of the compound), and cumulative dose of bone resorption therapy.
- cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures e.g. tooth extractions.

All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with romosozumab.

Atypical Femoral Fracture

Atypical low-energy or low-trauma fracture of the femoral shaft, which can occur spontaneously, has occurred rarely in patients receiving EVENITY in the clinical trials. Any patient who presents with new or unusual thigh, hip, or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of EVENITY therapy should be considered based on individual benefit-risk assessment.

4.5 Interactions with Other Medicaments and Other Forms of Interaction

No drug interaction studies have been conducted with EVENITY.

4.6 Special Populations

Pregnancy

Risk Summary

EVENITY is not indicated for use in women of reproductive potential or in pregnant women.

There are no studies of EVENITY in pregnant women. Therefore, it is not known whether EVENITY can cause foetal harm when administered to a pregnant woman.

Animal Data

Reproductive and developmental effects of romosozumab were assessed in the rat in a preliminary and definitive embryo foetal development study, a combined fertility and embryo development study, and a pre- and postnatal study.

In pregnant rats administered romosozumab at exposures at least 30-fold higher than the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg romosozumab (based on AUC comparison), romosozumab-related effects were limited to a slight increase in the incidence of reduced ventral processes on the sixth cervical vertebra in foetuses at Gestation Day 21, which resolved in pups examined postnatally. This variation represents a slight developmental delay in a skeletal process not found in humans, and therefore this finding is not relevant to humans.

Skeletal abnormalities (including syndactyly and polydactyly), occurred in 1 out of 75 litters across all studies. Based on the weight of evidence (including single litter incidence, below group mean exposure to romosozumab, presence of anti-romosozumab antibodies in the dam, and absence of skeletal malformations at substantially higher maternal and foetal exposures), these observations were concluded to be unrelated to romosozumab. There were no adverse effects on postnatal growth and development.

Syndactyly occurs at a high incidence in sclerosteosis but does not occur in patients heterozygous for the genetic mutation. Risk for malformations of developing digits in the human foetus is low following romosozumab exposure due to the timing of digit formation in the first trimester in humans, when placental transfer of immunoglobulins is limited.

Lactation

Romosozumab is not indicated for use in breast-feeding women.

It is not known whether EVENITY is present in human milk. Because many drugs are excreted in human milk and because of the potential for adverse effects in nursing infants from EVENITY, a decision should be made whether to discontinue nursing or discontinue EVENITY, taking into account the potential benefit of EVENITY to the mother or the potential benefit of breastfeeding to the infant.

Fertility

No data are available on the effect of EVENITY on human fertility. Animal studies in female and male rats did not show any effects on fertility endpoints at doses up to 300 mg/kg (100-fold the clinical dose) [see Preclinical Safety Data/Nonclinical Toxicology (5.3)].

Paediatrics

The safety and efficacy of EVENITY have not been established in paediatric patients [see Preclinical Safety Data/Nonclinical toxicology (5.3)].

Elderly

No dose adjustment is necessary in elderly patients (see also section 5.2).

Hepatic Impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment.

Renal Impairment

No dose adjustment is required in patients with renal impairment.

Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m^2) or receiving dialysis are at greater risk of developing hypocalcaemia [see Contraindications (4.3) and Special Warnings and Precautions for Use (4.4)]. Monitoring of calcium levels is highly recommended. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effect on the ability to drive or use heavy machinery have been performed in patients receiving EVENITY.

4.8 Adverse Reactions

Summary of the Safety Profile

The adverse reactions described in the table below are based on 12-month pooled data from 3695 postmenopausal women with osteoporosis and 163 men with osteoporosis treated with EVENITY in Phase II and Phase III, placebo-controlled clinical trials [see Adverse Reactions (4.8)]. The adverse reactions in EVENITY treated patients (N = 2040) in a double blind, Phase III active-controlled study were similar in type to those seen in the placebo-controlled trials. The most common adverse reactions (≥ 1/10) from the pooled safety data were viral upper respiratory tract infection and arthralgia.

Tabulated Summary of Adverse Reactions

Adverse reactions are displayed by system organ class and frequency below using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), and very rare (< 1/10,000).

Table 1. Tabulated Summary of Adverse Reactions

System Organ Class	Adverse Reactions	CIOMS Frequency
Infections and infestations	Viral upper respiratory tract infection	Very Common
Immune system disorders	Hypersensitivity[a]	Common
	Rash	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angio-oedema	Rare
	Erythema multiforme	Rare
Metabolism and nutrition disorders	Hypocalcaemia[b]	Uncommon
Nervous system disorders	Headache	Common
Respiratory, thoracic, and mediastinal disorders	Cough	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Very Common
	Neck pain	Common
	Muscle spasms	Common
General disorders and administration	Peripheral oedema	Common

site conditions	Injection site reactions[c]	Common

a. See Contraindications (4.3) and Special Warnings and Precautions for Use (4.4).
b. Defined as albumin adjusted serum calcium that was below the lower limit of normal. See Contraindications (4.3) and Special Warnings and Precautions for Use (4.4).
c. Most frequent injection site reactions were pain and erythema.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of romosozumab has been evaluated using a screening immunoassay for the detection of binding anti-romosozumab antibodies. For patients whose sera tested positive in the screening immunoassay, an *in vitro* assay was performed to detect neutralising antibodies.

In postmenopausal women dosed with 210 mg monthly EVENITY, the incidence of anti-romosozumab antibodies was 18.1% (1072 of 5914) for binding antibodies and 0.8% (50 of 5914) for neutralising antibodies. Across all doses studied in postmenopausal women, the pooled incidence of binding antibodies and neutralising antibodies was similar to the 210 mg monthly dose, respectively. In men with osteoporosis dosed with 210 mg monthly EVENITY, the incidence of anti-romosozumab antibodies was consistent [17.3% (28 of 162) for binding antibodies and 0.6% (1 of 162) for neutralising antibodies] with that observed in postmenopausal women with osteoporosis. No impact to the efficacy and safety of romosozumab was observed in the presence of anti-romosozumab antibodies.

Myocardial infarction, stroke and mortality

In the active-controlled trial of romosozumab for the treatment of severe osteoporosis in postmenopausal women during the 12-month double-blind romosozumab treatment phase, 16 women (0.8%) had myocardial infarction in the romosozumab arm versus 5 women (0.2%) in the alendronate arm and 13 women (0.6%) had stroke in the romosozumab arm versus 7 women (0.3%) in the alendronate arm. These events occurred in patients with and without a history of myocardial infarction or stroke. Cardiovascular death occurred in 17 women (0.8%) in the romosozumab group and 12 (0.6%) women in the alendronate group. The number of women with major adverse cardiac events (MACE = positively adjudicated cardiovascular death, myocardial infarction or stroke) was 41 (2.0%) in the romosozumab group and 22 (1.1%) in the alendronate group, yielding a hazard ratio of 1.87 (95% confidence interval [1.11, 3.14]) for romosozumab compared to alendronate. All-cause death occurred in 30 women (1.5%) in the romosozumab group and 22 (1.1%) women in the alendronate group.

In the placebo-controlled trial of romosozumab for the treatment of osteoporosis in postmenopausal women (including women with severe and less severe osteoporosis) during the 12-month double-blind romosozumab treatment phase, there was no difference in positively adjudicated MACE; 30 (0.8%) occurred in the romosozumab group and 29 (0.8%) in the placebo group. All-cause death occurred in 29 women (0.8%) in the romosozumab group and 24 (0.7%) women in the placebo group.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions as per local regulations.

4.9 Overdose

There is no experience with overdosage in clinical trials with EVENITY.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Other drugs affecting bone structure and mineralisation. ATC code: M05BX06

Mechanism of Action

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

Pharmacodynamic Effects

EVENITY has a dual effect on bone, increasing bone formation and decreasing bone resorption. In postmenopausal women with osteoporosis, EVENITY increased the bone formation marker procollagen type 1 N-terminal propeptide (P1NP) early in treatment, with a peak increase of approximately 145% relative to placebo 2 weeks after initiating treatment, followed by a return to placebo levels at month 9 and a decline to approximately 15% below placebo at month 12. EVENITY decreased the bone resorption marker type 1 collagen C-telopeptide (CTX) with a maximal reduction of approximately 55% relative to placebo 2 weeks after initiating treatment. CTX levels remained below placebo and were approximately 25% below placebo at month 12.

After discontinuation of EVENITY therapy in postmenopausal women with osteoporosis, P1NP levels returned to baseline within 12 months; CTX increased above baseline levels within 3 months and returned toward baseline levels by month 12, reflecting reversibility of effect. Upon retreatment with EVENITY after 12 months off treatment, the level of increase in P1NP and decrease in CTX by EVENITY was similar to that observed during the initial treatment.

In women transitioning from oral alendronate, EVENITY also increased bone formation and decreased bone resorption.

Clinical Data

Treatment of Osteoporosis in Postmenopausal Women

Study 1 (ARCH, alendronate-controlled) was a randomised, double blind, alendronate-controlled study of 4093 postmenopausal women aged 55 to 90 years (mean age of 74.3 years), with a median follow-up of 33 months.

The mean baseline lumbar spine, total hip, and femoral neck BMD T-scores were −2.96, −2.80, and −2.90, respectively, 96.1% of women had a vertebral fracture at baseline, and 99.8% of women had a previous fracture. Women were randomised (1:1) to receive either monthly subcutaneous injections of EVENITY (N = 2046) or oral weekly alendronate (N = 2047) for 12 months, with daily supplementation of calcium and vitamin D. After the 12-month treatment period, women in both arms transitioned to open-label alendronate while remaining blinded to their initial treatment. The primary analysis was performed when all women had completed the month 24 study visit and clinical fracture events were confirmed for at least 330 women, which occurred after a median of 33 months on study.

The primary efficacy endpoints were the incidence of new vertebral fracture through month 24 and the incidence of clinical fracture (defined as the composite of nonvertebral fracture and clinical vertebral fracture) at primary analysis. Secondary efficacy endpoints included the incidence of nonvertebral fractures, hip fractures, and major nonvertebral fractures at the primary analysis, and percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at month 12 and month 24.

Effect on New Vertebral and Clinical Fractures

EVENITY reduced the incidence of new vertebral fracture at 24 months and clinical fracture after a median of 33 months. The number of patients who experienced vertebral and clinical fracture was consistently lower in the EVENITY arm at prespecified time points. See Table 2 for full data.

Table 2. The Effect of EVENITY on the Incidence and Risk of New Vertebral and Clinical Fractures

	Alendronate/ Alendronate (N = 2047) n/N1 (%)	**Romosozumab/ Alendronate (N = 2046) n/N1 (%)**	**Absolute Risk Reduction (%) (95% CI)[a]**	**Relative Risk Reduction (%) (95% CI)[b]**	**Nominal p-value[c]**	**Adjusted p-value[d]**
Through Month 12						
New vertebral fracture	85/1703 (5.0)	55/1696 (3.2)	1.84 (0.51, 3.17)	36 (11, 54)	0.008	NA[e]
Clinical fracture	110/2047 (5.4)	79/2046 (3.9)	1.8 (0.5, 3.1)	28 (4, 46)	0.027	NA[e]
Through Month 24						
New vertebral fracture	147/1834 (8.0)	74/1825 (4.1)	4.03 (2.50, 5.57)	50 (34, 62)	< 0.001	< 0.001
Clinical fracture	197/2047 (9.6)	146/2046 (7.1)	2.7 (0.8, 4.5)	26 (9, 41)	0.005	NA[e]
After a median of 33 months						
Clinical fracture	266/2047 (13.0)	198/2046 (9.7)	NA	27 (12, 39)	< 0.001	< 0.001

For new vertebral fracture, N1 = Number of subjects in the primary analysis set for vertebral fractures.

a. Absolute risk reduction is based on the Mantel-Haenszel method (new vertebral fracture) or on inverse-weighted method (clinical fracture) adjusting for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline.

b. Relative risk reduction is based on the Mantel-Haenszel method adjusting for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline (new vertebral fracture) or Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline (clinical fracture).

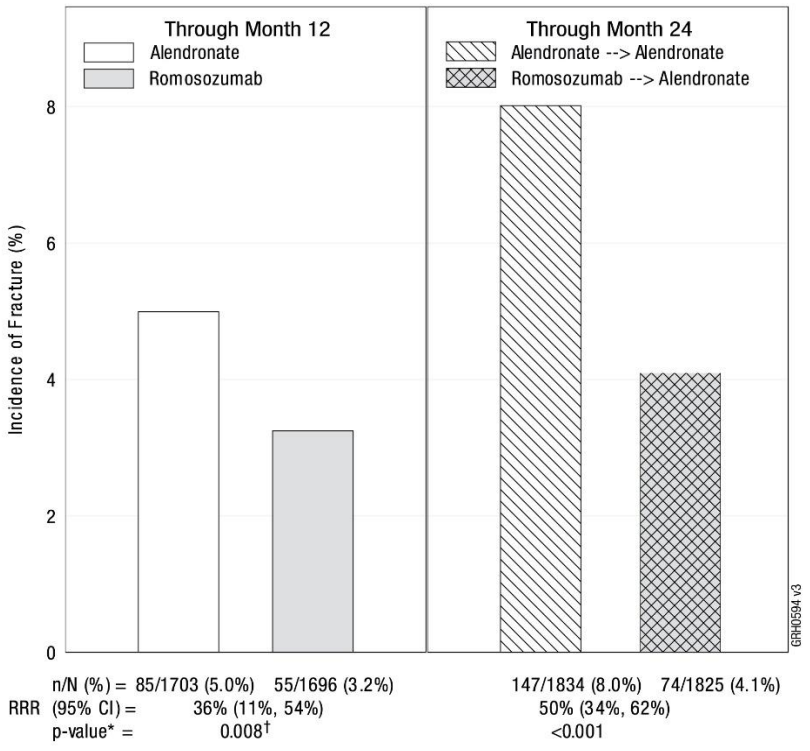
c. P-value is based on logistic regression model (new vertebral fracture) or Cox proportional hazards model (clinical fracture) adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.

d. Adjusted p-values are based on Hochberg procedure and are to be compared to a significance level of 0.05.

e. NA: Endpoint was not part of sequential testing strategy; therefore, p-value adjustment is not applicable.

EVENITY for 12 months followed by alendronate for 12 months demonstrated a persistent effect in reducing the incidence of new vertebral fractures (see Figure 1).

Figure 1. Effect of EVENITY on Incidence of New Vertebral Fractures through Month 12 and Month 24



N = Number of subjects in the primary analysis set for vertebral fractures
n = Number of subjects experiencing a fracture
Relative risk reduction (RRR) is based on the Mantel-Haenszel method adjusted for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline.
*p-values are based on separate logistic regression models adjusted for age strata, baseline total hip BMD T-score and presence of severe vertebral fracture at baseline.
† P-value does not meet multiplicity adjusted statistical significance.

Effect on Other Fracture Types/Groups

EVENITY significantly reduced the incidence of nonvertebral fracture after a median follow up of 33 months. EVENITY reduced the number of patients who experienced nonvertebral fracture, hip fracture, and major nonvertebral fractures compared to alendronate consistently at prespecified time points. See Table 3 for full data.

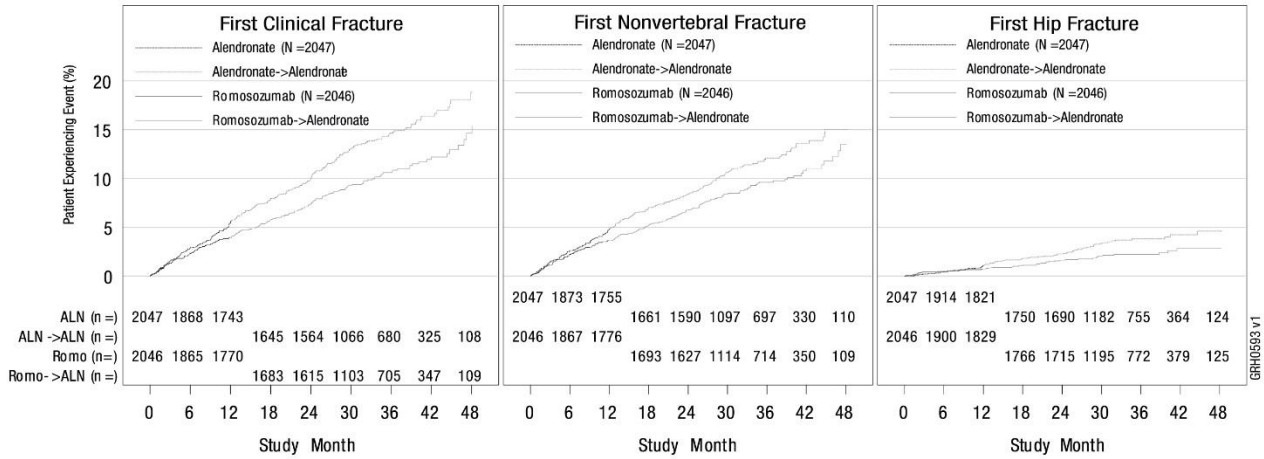
Table 3. Effect of EVENITY on the Incidence and Risk of Fractures

	Alendronate/ Alendronate (N = 2047) n/N1 (%)	Romosozumab/ Alendronate (N = 2046) n/N1 (%)	Absolute Risk Reduction (%) (95% CI)[a]	Relative Risk Reduction (%) (95% CI)[b]	Nominal p-value[c]	Adjusted p-value[d]
Through Month 12						
Nonvertebral fracture	95/2047 (4.6)	70/2046 (3.4)	1.4 (0.1, 2.6)	26 (-1, 46)	0.057	NA[f]
Hip fracture	22/2047 (1.1)	14/2046 (0.7)	0.3 (-0.3, .9)	36 (-26, 67)	0.19	NA[f]
Through Month 24						
Nonvertebral fracture	159/2047 (7.8)	129/2046 (6.3)	1.6 (-0.1, 3.3)	19 (-2, 36)	0.074	NA[f]
Hip fracture	43/2047 (2.1)	31/2046 (1.5)	0.6 (-0.2, 1.4)	28 (-15, 54)	0.17	NA[f]
After a median of 33 months						
Nonvertebral fracture	217/2047 (10.6)	178/2046 (8.7)	NA	19 (1, 34)	0.037	0.04
Hip fracture	66/2047 (3.2)	41/2046 (2.0)	NA	38 (8, 58)	0.015	NA[f]
Major nonvertebral fracture[e]	196/2047 (9.6)	146/2046 (7.1)	NA	27 (10, 41)	0.004	NA[f]

a. Absolute risk reduction is based on the inverse-weighted method adjusting for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline.
b. Relative risk reduction is based on the Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.
c. P-value based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.
d. Adjusted p-value is based on the Lan-DeMets alpha spending function and are to be compared to a significance level of 0.05.
e. Pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip, hip fracture, multiple new or worsening vertebral fracture, and clinical vertebral fracture.
f. NA: Endpoint was not part of sequential testing strategy; therefore, p-value adjustment is not applicable.

The Kaplan-Meier estimates of the cumulative incidence of clinical fracture, nonvertebral fracture and hip fracture over time are shown in Figure 2 below.

Figure 2. Cumulative Incidence of Clinical, Nonvertebral, and Hip Fractures



N = Number of subjects randomized
n = Number of subjects at risk for event at time point of interest

Effect on Bone Mineral Density (BMD)

EVENITY significantly increased BMD at the lumbar spine, total hip, and femoral neck compared with alendronate at month 12. At month 24, 12-month treatment with EVENITY followed by 12-month treatment with alendronate significantly increased BMD compared with alendronate alone for 24 months at the lumbar spine, total hip, and femoral neck. The BMD increase with EVENITY over alendronate observed at month 12 was maintained at month 24 (see Table 4).

Table 4. Mean Percent Change in BMD from Baseline through Month 12 and Month 24

	Alendronate Mean (95% CI) N = 2047	**Romosozumab Mean (95% CI) N = 2046**	**Treatment Difference from Alendronate**
At Month 12			
Lumbar spine	5.0 (4.73, 5.21)	13.7 (13.36, 13.99)	8.7[a] (8.31, 9.09)
Total hip	2.8 (2.67, 3.02)	6.2 (5.94, 6.39)	3.3[a] (3.03, 3.60)
Femoral neck	1.7 (1.46, 1.98)	4.9 (4.65, 5.23)	3.2[a] (2.90, 3.54)
	Alendronate/Alendronate Mean (95% CI) N = 2047[a]	**Romosozumab/Alendronate Mean (95% CI) N = 2046[a]**	**Treatment Difference from Alendronate/Alendronate**
At Month 24			
Lumbar spine	7.2 (6.90, 7.53)	15.3 (14.89, 15.69)	8.1[a] (7.58, 8.57)
Total hip	3.5 (3.23, 3.68)	7.2 (6.95, 7.48)	3.8[a] (3.42, 4.10)
Femoral neck	2.3 (1.96, 2.57)	6.0 (5.69, 6.37)	3.8[a] (3.40, 4.14)

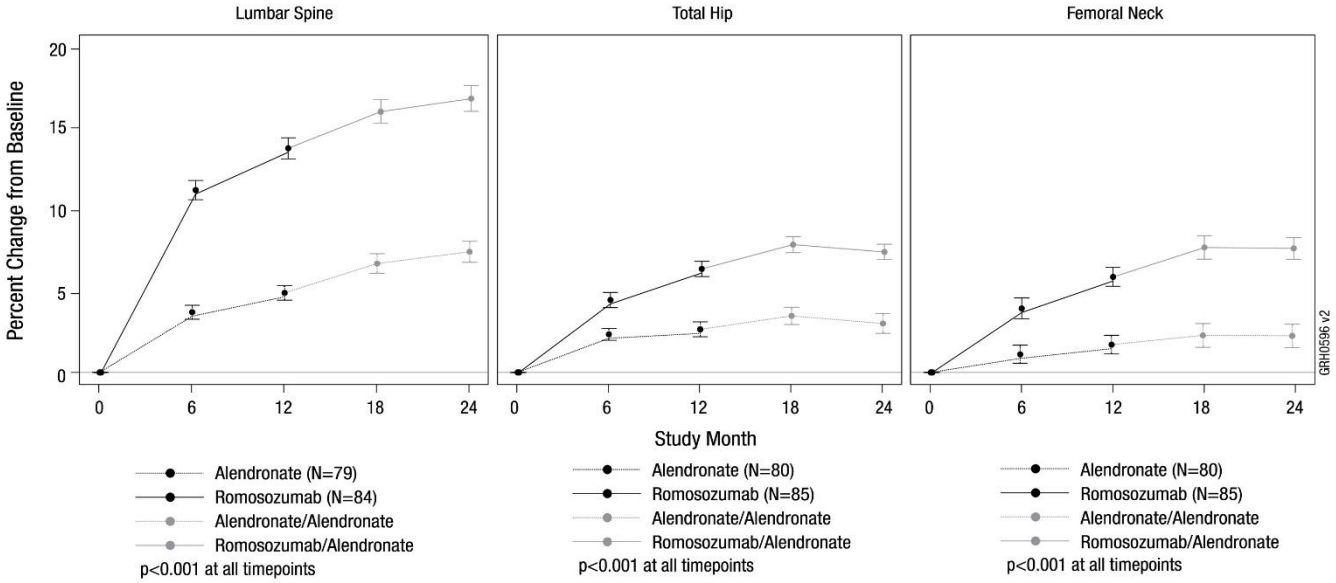
a. P-value < 0.001 based on an ANCOVA model, adjusting for treatment, age strata, presence of severe vertebral fracture at baseline, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction.

A total of 167 subjects participated in the imaging component (as measured by DXA) of the Imaging and PK/BTM/Biomarker Substudy. EVENITY resulted in progressive increases from baseline in BMD beginning at month 6. Treatment differences in BMD between EVENITY and alendronate groups continued to increase at month 12. After transitioning to alendronate after 12-month treatment with EVENITY, treatment differences in BMD between the EVENITY-alendronate and alendronate-alendronate groups continued to increase at month 18 and were maintained at month 24 (see Figure 3).

Consistent effects on BMD were observed regardless of baseline age, baseline BMD, and geographic region at the lumbar spine, total hip, and femoral neck.

Treatment differences in BMD at 6 months were 7.6% at the lumbar spine, 2.2% at the total hip, and 2.9% at the femoral neck. At 12 months, the treatment differences were 8.9% at the lumbar spine, 3.7% at the total hip, and 4.1% at the femoral neck. At 18 months, after transitioning to alendronate after 12 months of EVENITY treatment, the treatment differences between the EVENITY-alendronate and alendronate-alendronate groups were 9.3% at the lumbar spine, 4.3% at the total hip, and 5.4% at the femoral neck. At 24 months, the EVENITY-alendronate group maintained gains in BMD compared to on the alendronate-alendronate group, with treatment differences of 9.4% at the lumbar spine, 4.3% at the total hip, and 5.3% at the femoral neck.

Figure 3. Percent Change in BMD at Lumbar Spine, Total Hip, and Femoral Neck from Baseline Over 24 Months



N = Number of randomized subjects enrolled in the sub-study with values at baseline and at least one post-baseline visit at Month 6 or Month 18
n = Number of subjects with evaluable data at the time point of interest
Point estimates, 95% confidence intervals, and p-values are based on ANCOVA model adjusting for treatment, presence of severe vertebral fracture at baseline, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction. P-value is for difference in treatment effect.
Missing values are imputed by carrying forward the last non-missing post-baseline value prior to the missing value and within the treatment period.

Study 2 (FRAME, placebo-controlled) was a randomised, double blind, placebo-controlled study of 7180 postmenopausal women aged 55 to 90 years (mean age of 70.9 years). The mean baseline lumbar spine, total hip, and femoral neck BMD T-scores were 2.72, −2.47, and –2.75, respectively, and 18.3% of women had a vertebral fracture at baseline.

Women were randomised to receive subcutaneous injections of either EVENITY (N = 3589) or placebo (N = 3591) once every month for 12 months with daily supplementation of calcium and vitamin D. After the 12-month treatment period, women in both arms transitioned to open-label denosumab 60 mg subcutaneous every 6 months for 12 months while remaining blinded to initial treatment.

The co primary efficacy endpoints were the incidence of new vertebral fractures through month 12 and through month 24. Secondary efficacy endpoints included the incidence of clinical fractures (all symptomatic fractures including nonvertebral and painful vertebral fractures), nonvertebral fractures, new or worsening vertebral fractures, major nonvertebral fractures, hip fractures, and percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck, and were evaluated though 24 months.

Effect on New Vertebral and Clinical Fractures

EVENITY significantly reduced the incidence of new vertebral fractures through month 12 ($p < 0.001$), as shown in Table 5. The reduction in fracture risk persisted through the second year in women who received EVENITY during the first year and transitioned to denosumab compared to those who transitioned from placebo to denosumab (month 24; $p < 0.001$).

EVENITY also significantly reduced the incidence of clinical fractures through month 12 (see Table 5 and Figure 4 for time to first clinical fracture).

Table 5. The Effect of EVENITY on the Incidence and Risk of New Vertebral and Clinical Fractures through Month 12 and Month 24

	Proportion of Women with Fracture					
	Placebo (N = 3591) n/N1 (%)	Romosozumab (N = 3589) n/N1 (%)	Absolute Risk Reduction (%) (95% CI)[a]	Relative Risk Reduction (%) (95% CI)[b]	Nominal p-value[c]	Adjusted p-value[d]
Through Month 12						
New vertebral	59/3322 (1.8)	16/3321 (0.5)	1.30 (0.79, 1.80)	73 (53, 84)	< 0.001	< 0.001
Clinical	90/3591 (2.5)	58/3589 (1.6)	1.2 (0.4, 1.9)	36 (11, 54)	< 0.008	0.008
	Placebo/ Denosumab (%)	**Romosozumab/ Denosumab (%)**				
Through Month 24						
New vertebral[b]	84/3327 (2.5)	21/3325 (0.6)	1.89 (1.30, 2.49)	75 (60, 84)	< 0.001	< 0.001
Clinical	147/3591 (4.1)	99/3589 (2.8)	1.4 (0.5, 2.4)	33 (13, 48)	0.002	0.096

For new vertebral fracture, N1 = Number of subjects in the primary analysis set for vertebral fractures.

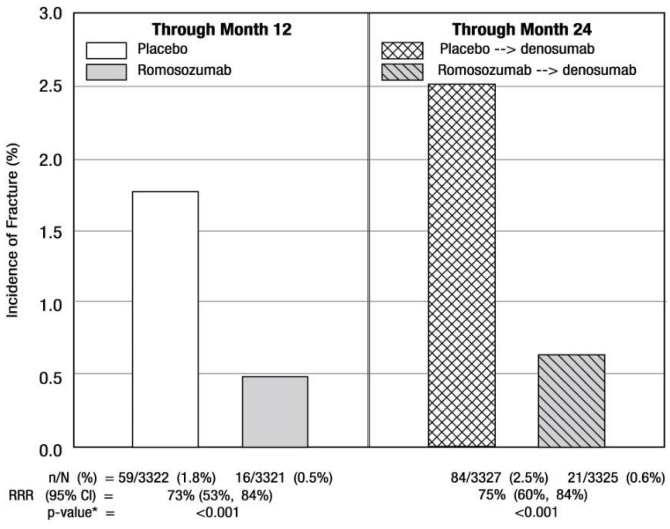
a. Absolute risk reduction is based on the Mantel-Haenszel method (new vertebral fracture) or on inverse-weighted method (clinical fracture) adjusting for age and prevalent vertebral fracture strata.

b. Relative risk reduction is based on the Mantel-Haenszel method (new vertebral fracture) or Cox proportional hazards model (clinical fracture) adjusting for age and prevalent vertebral fracture strata.

c. P-value based on logistic regression model (new vertebral fracture) or Cox proportional hazards model (clinical fracture) adjusting for age and prevalent vertebral fracture strata.

d. Adjusted p-values are based on Hochberg procedure and fixed sequence testing procedure and are to be compared to a significance level of 0.05.

Figure 4. Effect of EVENITY on Incidence of New Vertebral Fractures through Month 12 and Month 24



N = Number of subjects in the primary analysis set for vertebral structures
n = Number of subjects experiencing a fracture
Relative risk reduction (RRR) is based on the Mantel-Haenszel method adjusting for age and prevalent vertebral fracture stratification variables
*p-values are based on separate logistic regression models adjusted for age and prevalent vertebral fracture stratification variables.

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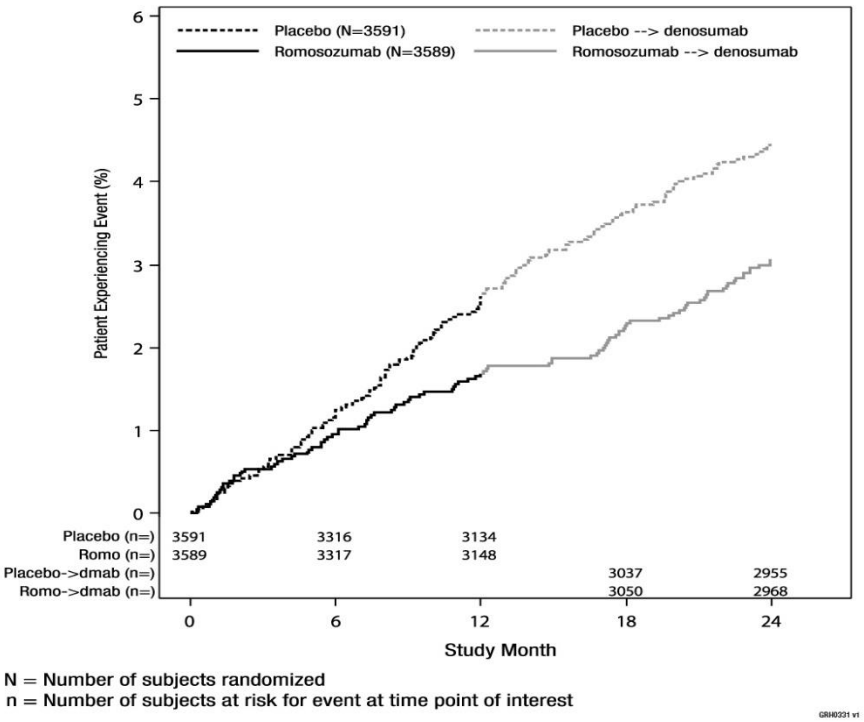
Figure 5. Cumulative Incidence of Clinical Fractures through Month 24



N = Number of subjects randomized
n = Number of subjects at risk for event at time point of interest

Effect on Other Fracture Types/Groups

Please see Table 6 for effect of EVENITY on other Fracture Types/Groups through month 24.

Table 6. The Effect of EVENITY on the Incidence and Risk of Other Fracture Types/Groups through Month 12 and Month 24

	Proportion of Women with Fracture					
	Placebo (N = 3591) n/N1 (%)	Romosozumab (N = 3589) n/N1 (%)	Absolute Risk Reduction (%) (95% CI)[a]	Relative Risk Reduction (%) (95% CI)[b]	Nominal p-value[c]	Adjusted p-value[d]
Through Month 12						
Nonvertebral	75/3591 (2.1)	56/3589 (1.6)	0.8 (0.1, 1.4)	25 (−5, 47)	0.096	0.096
Major nonvertebral	55/3591 (1.5)	37/3589 (1.0)	0.6 (0.1, 1.2)	33 (−2, 56)	0.060	0.096
New or worsening vertebral	59/3322 (1.8)	17/3321 (0.5)	1.3 (0.76, 1.8)	71 (51, 83)	< 0.001	0.096
Hip	13/3591 (0.4)	7/3589 (0.2)	0.3 (0.0, 0.6)	46 (−35, 78)	0.18	0.18
Major osteoporotic	63/3591 (1.8)	38/3589 (1.1)	0.9 (0.3, 1.5)	40 (10, 60)	0.012	NA[e]
Multiple new/worsening vertebral	9/3322 (0.3)	1/3321 (< 0.1)	0.24 (0.05, 0.4)	89 (13, 99)	0.011	NA[e]
	Placebo/ Denosumab (%)	**Romosozumab/ Denosumab (%)**				
Through Month 24						
Nonvertebral	129/3591 (3.6)	96/3589 (2.7)	1.0 (0.2, 1.9)	25 (3, 43)	0.029	0.057
Major nonvertebral	101/3591 (2.8)	67/3589 (1.9)	1.1 (0.3, 1.8)	33 (9, 51)	0.009	0.096
New or worsening vertebral	84/3327 (2.5)	22/3325 (0.7)	1.86 (1.27, 2.5)	74 (58, 84)	< 0.001	0.096
Hip	22/3591 (0.6)	11/3589 (0.3)	0.4 (0.0, 0.7)	50 (−4, 76)	0.059	0.12
Major osteoporotic	110/3591 (3.1)	68/3589 (1.9)	1.2 (0.5, 2.0)	38 (16, 54)	0.002	NA[e]
Multiple new/worsening vertebral	17/3327 (0.5)	1/3325 (< 0.1)	0.48 (0.23, 0.7)	94 (56, 99)	< 0.001	NA[e]

For vertebral fracture endpoints, N1 = Number of subjects in the primary analysis set for vertebral fractures.

a. Absolute risk reduction is based on the Mantel-Haenszel method (vertebral fracture endpoints) or on inverse-weighted method (other fracture endpoints) adjusting for age and prevalent vertebral fracture strata.
b. Relative risk reduction is based on the Mantel-Haenszel method (vertebral fracture endpoints) or Cox proportional hazards model (other fracture endpoints) adjusting for age and prevalent vertebral fracture strata.
c. P-value based on logistic regression model (vertebral fracture endpoints) or Cox proportional hazards model (other fracture endpoints) adjusting for age and prevalent vertebral fracture strata.
d. Adjusted p-values are based on Hochberg procedure and fixed sequence testing procedure and are to be compared to a significance level of 0.05.
e. NA: Endpoint was not part of sequential testing strategy; therefore, p-value adjustment is not applicable.

Effect on Bone Mineral Density (BMD)

EVENITY significantly increased BMD at the lumbar spine, total hip, and femoral neck compared to placebo at month 12. Following 12 months of treatment, EVENITY increased BMD at the lumbar spine from baseline in 99% of postmenopausal women. Ninety-two percent of women treated with EVENITY achieved at least a 5% increase from baseline in BMD at lumbar spine by month 12 and 68% gained 10% or more. These effects were sustained with transition to another osteoporosis treatment; women who received EVENITY for 12 months followed by denosumab for 12 months had greater increases in BMD at the lumbar spine, total hip, and femoral neck at month 24 compared to women who received placebo for 12 months followed by denosumab for 12 months (see Table 7).

Consistent effects on BMD were observed regardless of baseline age, baseline BMD, and geographic region at the lumbar spine, total hip, and femoral neck.

Table 7. Mean Percent Change in BMD from Baseline through Month 12 and Month 24

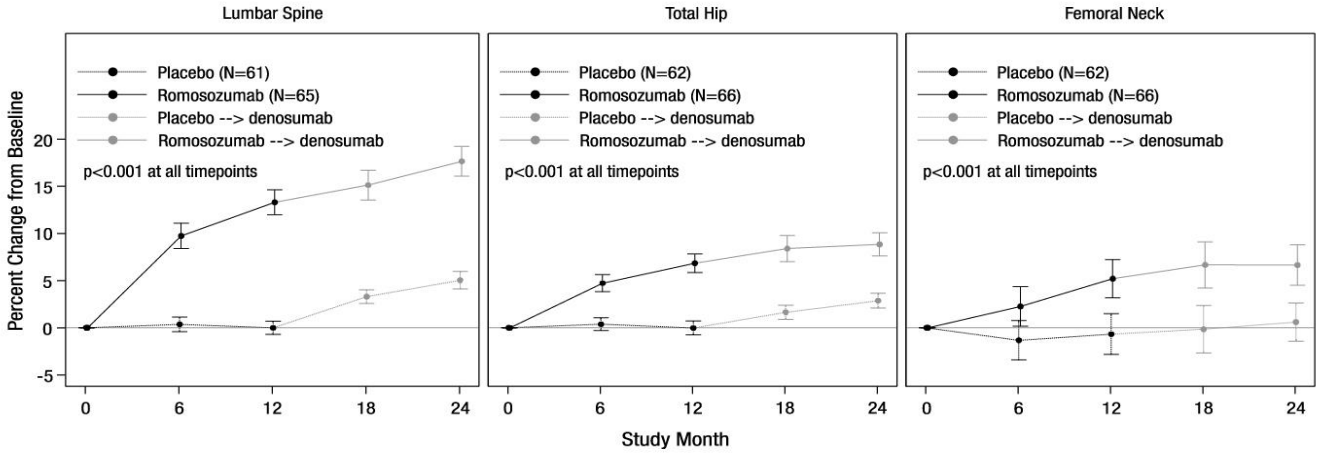
	Placebo Mean (95% CI) N = 3591[a]	**Romosozumab Mean (95% CI) N = 3589[a]**	**Treatment Difference from Placebo Mean (95% CI)**
At Month 12			
Lumbar spine	0.4 (0.2, 0.5)	13.1 (12.8, 13.3)	12.7[b] (12.4, 12.9)
Total hip	0.3 (0.1, 0.4)	6.0 (5.9, 6.2)	5.8[b] (5.6, 6.0)
Femoral neck	0.3 (0.1, 0.5)	5.5 (5.2, 5.7)	5.2[b] (4.9, 5.4)
	Placebo/Denosumab Mean (95% CI) N = 3591[a]	**Romosozumab/Denosumab Mean (95% CI) N = 3589[a]**	**Treatment Difference from placebo/Denosumab**
At Month 24			
Lumbar spine	5.5 (5.3, 5.7)	16.6 (16.3, 16.8)	11.1[b] (10.8, 11.4)
Total hip	3.2 (3.1, 3.3)	8.5 (8.3, 8.7)	5.3[b] (5.1, 5.5)
Femoral neck	2.3 (2.1, 2.6)	7.3 (7.0, 7.5)	4.9[b] (4.7, 5.2)

a. Number of women randomised.
b. p-value < 0.001 based on an ANCOVA model, adjusting for treatment, age and prevalent vertebral fracture strata, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction.

Among women with BMD assessed at baseline and every 6 months, EVENITY significantly increased BMD at the lumbar spine, total hip, and femoral neck relative to placebo at 6 and 12 months. Following the transition from EVENITY to denosumab, BMD continued to increase through month 24. In women who transitioned from placebo to denosumab, BMD also increased with denosumab use. The differences in BMD achieved at month 12 between EVENITY and placebo patients were overall maintained at month 24, when comparing patients who transitioned from EVENITY to denosumab versus patients who transitioned from placebo to denosumab (see Figure 6).

Treatment differences in BMD at 6 months were 9.4% at the lumbar spine, 4.3% at the total hip, and 3.6% at the femoral neck. After 12 months, the treatment differences were 13.3% at the lumbar spine, 6.9% at the total hip, and 5.9% at the femoral neck. At 18 months, women who received EVENITY followed by denosumab maintained gains in BMD compared to women who received placebo followed by denosumab, with treatment differences of 11.8% at the lumbar spine, 6.8% at the total hip, and 6.8% at the femoral neck. At 24 months, women who received EVENITY followed by denosumab maintained gains in BMD compared to women who received placebo followed by denosumab, with treatment differences of 12.6% at the lumbar spine, 6.0% at the total hip, and 6.0% at the femoral neck.

Figure 6. Percent Change in BMD at Lumbar Spine, Total Hip, and Femoral Neck from Baseline Over 24 Months



N = Number of randomized subjects enrolled in the lumbar spine and proximal femur DXA substudy with values at baseline and at least one post-baseline visit
Point estimates 95% confidence intervals, and p-values are based on ANCOVA model adjusting for treatment, baseline value, machine type, and baseline-by-machine type interaction. P-value is for difference in treatment effect.
Missing values are imputed by carrying forward the last non-missing post-baseline value prior to the missing value and within the study period.

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Bone Histology and Histomorphometry

A total of 154 transiliac crest bone biopsy specimens were obtained from 139 postmenopausal women with osteoporosis at month 2, month 12, and/or month 24. Of the biopsies obtained, 154 (100.0%) were adequate for qualitative histology and 138 (89.6%) were adequate for full quantitative histomorphometry assessment. Qualitative histology assessments from those treated with EVENITY showed normal bone architecture and quality at all time points. There was no evidence of woven bone, mineralisation defects, or marrow fibrosis.

Histomorphometry assessments on biopsies at months 2 and 12 compared the effect of EVENITY with placebo (15 specimens at month 2 and 39 specimens at month 12 in the EVENITY group, 14 specimens at month 2 and 31 specimens at month 12 in the placebo group). At month 2 in women treated with EVENITY, histomorphometric indices of bone formation at trabecular and endocortical surfaces were increased due to a significant increase in modelling based formation with no significant effect on remodelling formation. These effects on bone formation were accompanied by a decrease in indices of bone resorption. At month 12, both bone formation and resorption indices were decreased with EVENITY, while bone volume and trabecular and cortical thickness were increased. Biopsies obtained at month 24 compared the effect of EVENITY for 12 months followed by denosumab for 12 months (18 specimens) with placebo followed by denosumab (21 specimens). At month 24, indices of bone remodelling were low and similar in both groups, consistent with the effects of denosumab.

Treatment of Osteoporosis in Women Transitioning from Bisphosphonate Therapy

Study 3 (STRUCTURE) was a randomised, open-label study of 436 postmenopausal women aged 56 to 90 years (mean age of 71.5 years) with osteoporosis transitioning from bisphosphonate therapy to EVENITY. This study evaluated safety and BMD changes by dual-energy X-ray absorptiometry (DXA) through 12 months of treatment with EVENITY compared with 12 months of treatment with teriparatide. The study also evaluated hip strength estimated by finite element analysis (FEA) over 12 months using quantitative computed tomography images.

Enrolled women had a mean baseline lumbar spine, total hip, and femoral neck BMD T-scores of –2.85, −2.24, and –2.46, respectively and a history of nonvertebral fracture after age 50 or vertebral fracture at any time.

At month 12, EVENITY increased BMD from baseline by 9.8% (95% CI: 9.0, 10.5) at the lumbar spine, 2.9% (95% CI: 2.5, 3.4) at the total hip, and 3.2% (95% CI: 2.6, 3.8) at the femoral neck. Treatment differences in BMD at 12 months compared to teriparatide were 4.4% (95% CI: 3.4, 5.4) at the lumbar spine,

3.4% (95% CI: 2.8, 4.0) at the total hip, and 3.4% at the femoral neck (95% CI: 2.6, 4.2; p-value < 0.0001 for all comparisons).

At month 12, EVENITY increased estimated strength from baseline by 2.5% (95% CI: 1.7, 3.2) at the total hip. The treatment difference in estimated strength at the total hip at month 12 compared to teriparatide was 3.2% (95% CI: 2.1, 4.3; p-value < 0.0001).

Adverse reactions observed in this study were generally consistent with those seen in women not transitioning from bisphosphonate therapy (discussed in Section 4.8).

5.2 Pharmacokinetic Properties

Following SC administration, romosozumab exhibits nonlinear pharmacokinetics as a result of binding to sclerostin. Dose proportional increases in exposure were observed for the doses of 140 mg and higher.

Administration of a single dose of 210 mg romosozumab in healthy male and female subjects (N = 90, age range: 21 to 65 years) resulted in a mean (standard deviation [SD]) maximum serum concentration (C_{max}) of 22.2 (5.8) mcg/mL and a mean area under the concentration-time curve (AUC) of 389 (127) mcg*day/mL. The median time to maximum romosozumab concentration (T_{max}) was 5 days (range: 2 to 7 days).

Following a 210 mg subcutaneous dose, bioavailability was 81%. After C_{max}, serum levels declined with a mean effective half-life of 12.8 days. Steady state was generally reached by month 3 with minimal accumulation (less than 2-fold) following monthly dosing.

The presence of anti-romosozumab binding antibodies decreased romosozumab exposure up to 22%, which was not considered clinically meaningful [see Adverse Reactions (4.8)].

Based on a population pharmacokinetic analysis, age (20–89 years), gender, race, or disease state (low bone mass or osteoporosis) had no clinically meaningful effects on pharmacokinetics (< 20% change in exposure at steady state). Romosozumab exposure decreased with increasing body weight. This decrease had a minimal impact on lumbar spine BMD gain (< 15% change) based on exposure response analyses and was not considered clinically meaningful. Thus, no dose adjustment is necessary based on age, gender, race, disease state, or body weight.

The pharmacokinetics of romosozumab were similar in patients transitioning from bisphosphonate therapy.

Drug Interactions

No drug drug interaction studies have been conducted with romosozumab.

Special Populations

Paediatrics:
The pharmacokinetics of romosozumab in paediatric patients have not been assessed.

Elderly:
The pharmacokinetics of romosozumab were not affected by age from 20 to 89 years.

Renal Impairment:
Following a single 210 mg dose of romosozumab in a clinical study of 16 patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) or end-stage renal disease (ESRD) requiring haemodialysis, mean C_{max} and AUC were 29% and 44% higher in patients with severe renal impairment as compared to healthy subjects. Mean romosozumab exposure was similar between patients with ESRD requiring haemodialysis and healthy subjects.

A population pharmacokinetic analysis indicated an increase in romosozumab exposure with increasing severity of renal impairment. However, based on both the renal impairment study and population PK

analysis, this increase is not clinically meaningful and no dose adjustment is necessary in these patients [see Special Populations (4.6)].

Hepatic Impairment:
No clinical studies have been conducted to evaluate the effect of hepatic impairment.

5.3 Preclinical Safety Data/Nonclinical Toxicology

Carcinogenicity

In a carcinogenicity study, doses up to 50 mg/kg/week were administered by subcutaneous injection to Sprague-Dawley male and female rats from 8 weeks to up to 98 weeks of age. These doses resulted in systemic exposures that were up to 19 times higher than the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg romosozumab (based on AUC comparison). Romosozumab caused a dose-dependent increase in bone mass with macroscopic bone thickening at all doses. There were no effects of romosozumab on mortality or tumour incidence in male or female rats.

Mutagenicity

Mutagenesis has not been evaluated, as monoclonal antibodies are not expected to alter DNA or chromosomes.

Impairment of Fertility

No effects on fertility were observed in male and female rats at doses up to 300 mg/kg (100 times the clinical dose). No effects were noted in reproductive organs in rats and cynomolgus monkeys dosed with romosozumab in the 6-month chronic toxicology studies at exposures up to 37 and 90 times higher, respectively, than the systemic exposure observed in humans administered 210 mg romosozumab monthly (based on AUC comparison).

Animal Toxicology and/or Pharmacology

No adverse effects were noted in rats and monkeys after 26 once weekly subcutaneous injections at doses up to 100 mg/kg and systemic exposures 37 and 90 times higher, respectively, than the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg romosozumab (based on AUC comparison).

In growing rats administered a rodent surrogate sclerostin antibody at pharmacologically active doses, a transient increase in longitudinal growth rate predicted to result in < 1% increase in bone length was observed. In growing rats dosed with romosozumab for 6 months resulting in exposures up to 19 times higher than the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg romosozumab (based on AUC comparison), there was no effect on femur length.

In bone safety studies in ovariectomised rats and monkeys, once weekly treatment with romosozumab for 12 months increased bone formation and decreased bone resorption. The resulting increase in bone mass and improvements in cortical bone geometry and cancellous bone microarchitecture was associated with increased bone strength at exposures from 0.5 to 21 times higher than the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg romosozumab (based on AUC comparison). Bone tissue was of normal or improved quality with no evidence of mineralisation defects, accumulation of osteoid, or woven bone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Each single use pre-filled syringe containing 105 mg romosozumab in 1.17 mL solution (90 mg/mL) contains:

0.61 mg calcium
3.8 mg acetate
70 mg sucrose
0.07 mg polysorbate 20
Water for Injection
Sodium hydroxide to pH of 5.2

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

The expiry date is indicated on the packaging.

6.4 Special Precautions for Storage

Refrigerate at 2°C to 8°C in the original carton.
If removed from the refrigerator, EVENITY should be kept at controlled room temperature (up to 25°C) in the original carton and must be used within 30 days.
Protect EVENITY from direct light and do not expose to temperatures above 25°C.
Do not freeze.
Do not store EVENITY in extreme heat or cold.
Do not shake.

6.5 Nature and Contents of Container

Sterile, preservative-free, clear to opalescent, colourless to light yellow solution, pH 5.2.

The pre-filled syringe is not made with natural rubber latex.

EVENITY is provided as:

- 1.17 mL solution in a single use Crystal Zenith® pre-filled syringe (90 mg/mL PFS); supplied as a 2-pack.

6.6 Special Precautions for Disposal and Other Handling

Before administration, the solution should be inspected. Do not inject the solution if it contains particles, or is cloudy or discoloured. To avoid discomfort at the site of injection, allow the medicine to reach room temperature (up to 25°C) before injecting. Inject the entire contents.

Prior to subcutaneous administration, allow EVENITY to sit at room temperature for at least 30 minutes before injecting. Do not warm in any other way.

Visually inspect the solution for particles and discolouration. Do not use if the solution is discoloured, cloudy, or contains particles.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Comprehensive instructions for the administration of EVENITY are provided in the "Instructions for Use".

7. PRODUCT OWNER

Amgen Inc.
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8. DATE OF REVISION OF THE TEXT

May 2021

SGEVEPI01