WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION, STROKE AND CARDIOVASCULAR DEATH

- **EVENITY may increase the risk of myocardial infarction, stroke and cardiovascular death *[see Warnings and Precaution (4.4)].* EVENITY should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year. Consider whether the benefits outweigh the risks in patients with a history of MI or stroke and other cardiovascular risk factors. If a patient experiences a myocardial infarction or stroke during therapy, EVENITY should be discontinued.**

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 List of Excipients (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 in treatment of severe osteoporosis in postmenopausal women at high risk of fracture (see section 5.1).

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 Pharmacodynamic properties, 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 an antiresorptive osteoporosis therapy [see Pharmacodynamic properties, clinical data (5.1)]. Treatment should be initiated and supervised by specialist

physicians experienced in the management of osteoporosis. After initial training in proper subcutaneous injection technique, an individual may self-inject EVENITY if a physician determines that is appropriate and with medical follow-up as necessary.
The efficacy and safety of treatment with EVENITY for longer than 12 months has not been established.

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 discolouration 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)].

4.4 Special Warnings and Precautions for Use

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)].

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)].

Myocardial Infarction, Stroke and Cardiovascular Death

In a randomized 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.
In two large, controlled fracture trials of EVENITY for the treatment of osteoporosis in postmenopausal women, cardiovascular events of myocardial infarction (MI) and stroke were prospectively adjudicated. In the active-controlled trial (N = 4054) during the 12-month double blind EVENITY treatment phase, MI occurred in 16 women (0.8%) in the EVENITY arm and 5 (0.2%) in the alendronate arm; stroke occurred in 13 women (0.6%) in the EVENITY arm and 7 (0.3%) in the alendronate arm. These events occurred in patients with and without a history of MI or stroke. In the placebo-controlled trial (N = 7157) during the 12-month double blind EVENITY treatment phase, MI occurred in 9 women (0.3%) in the EVENITY arm and 8 (0.2%) in the placebo arm; stroke occurred in 8 women (0.2%) in the EVENITY arm and 10 (0.3%) in the placebo arm. These events occurred in patients with and without a history of MI or stroke.

A causal relationship between EVENITY and these events has not been established. In both trials, most participants had common risk factors for cardiovascular disease, and within each trial, cardiovascular risk factors were balanced between treatment arms. Consider the benefit-risk in patients at increased risk for MI or stroke. Patients should be instructed to watch for symptoms of MI and stroke and to seek prompt medical attention if symptoms occur. If a patient experiences a myocardial infarction or stroke during therapy, consider discontinuation of EVENITY.

EVENITY should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year. Treating physician should assess patient for risk of CV before treatment.

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.

Prior to treatment, a dental examination with appropriate preventative dentistry should be considered in patients with possible risk factors. Before commencing invasive dental procedures, patients and their dentist should be advised of the risks and reports of osteonecrosis of the jaw so that dental symptoms, including toothache, developing during treatment can be fully assessed for cause before treatment of the tooth commences.

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.

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. In animal reproduction studies, weekly administration of romosozumab to pregnant rats during the period of organogenesis at exposures greater than 31 times the clinical exposure produced skeletal abnormalities in the offspring. Administration of romosozumab to rats prior to mating and through to the end of lactation produced minimal to slight decreases in femoral bone mineral density and/or cortical circumferences in the offspring at 1.4 to 54 times the expected exposure in humans *[see Data]*.

Data
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 development study.

Skeletal malformations including syndactyly and polydactyly occurred in 1 out of 75 litters across all rat reproductive toxicity studies, in the litter of a dam given weekly subcutaneous romosozumab doses of 300 mg/kg (equivalent to at least 31 times the clinical exposure observed in humans following a monthly subcutaneous dose of 210 mg, based on area under the concentration-time curve [AUC] comparison).

In the offspring of female rats given weekly romosozumab doses from 6 weeks before cohabitation through mating and lactation, femoral periosteal and endocortical circumferences were slightly decreased at 10, 60, and 300 mg/kg (equivalent to 1.4, 18, and 54 times the clinical exposure following a monthly subcutaneous dose of 210 mg, based on AUC comparison). Cortical thickness was increased at 300 mg/kg (equivalent to 54 times expected clinical exposure). Femoral metaphyseal bone mineral density was slightly decreased at 60 and 300 mg/kg (equivalent to 18 and 54 times expected clinical exposure).

Lactation

Risk Summary
EVENITY is not indicated for use in women of reproductive potential. In animal studies where pregnant rats were given weekly doses of romosozumab from 6 weeks before cohabitation through mating and lactation at 10, 60, or 300 mg/kg (equivalent to 1.4, 18 or 54 times the clinical exposure following a monthly subcutaneous dose of 210 mg, based on AUC comparison), romosozumab was dose-dependently present in the serum of offspring on postnatal day 21 at 0.01 to 2.4 times maternal exposure due to gestational and/or lactational exposure.

Paediatrics

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

Geriatrics

Of the 6525 postmenopausal women with osteoporosis treated with EVENITY in clinical studies, 5222 (80%) were ≥ 65 years old and 2385 (36.6%) were ≥ 75 years old. No overall differences in safety or efficacy were observed among these patients and younger patients.

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. There is limited experience in patients with eGFR < 30 mL/min.

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 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

System Organ Class	Adverse Reactions	CIOMS Frequency
General disorders and administration site conditions	Peripheral oedema	Common
	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. No impact to the efficacy and safety of romosozumab was observed in the presence of anti-romosozumab antibodies.

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.

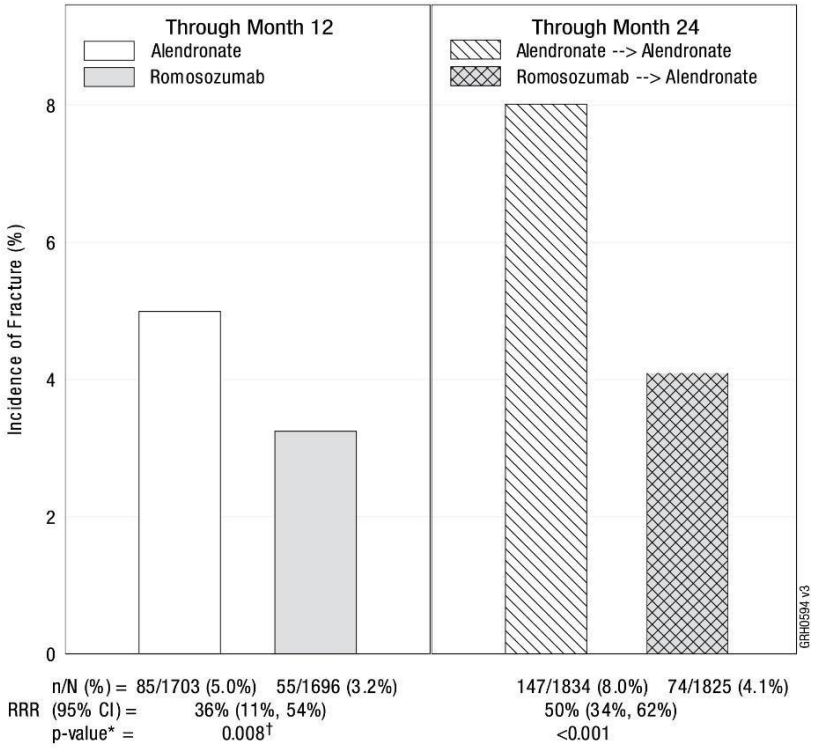
a. Absolute risk reduction is based on the Mantel-Haenszel method (new vertebral fracture) or on inverse-weighted method (clinical fracture) adjusting for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline.

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.

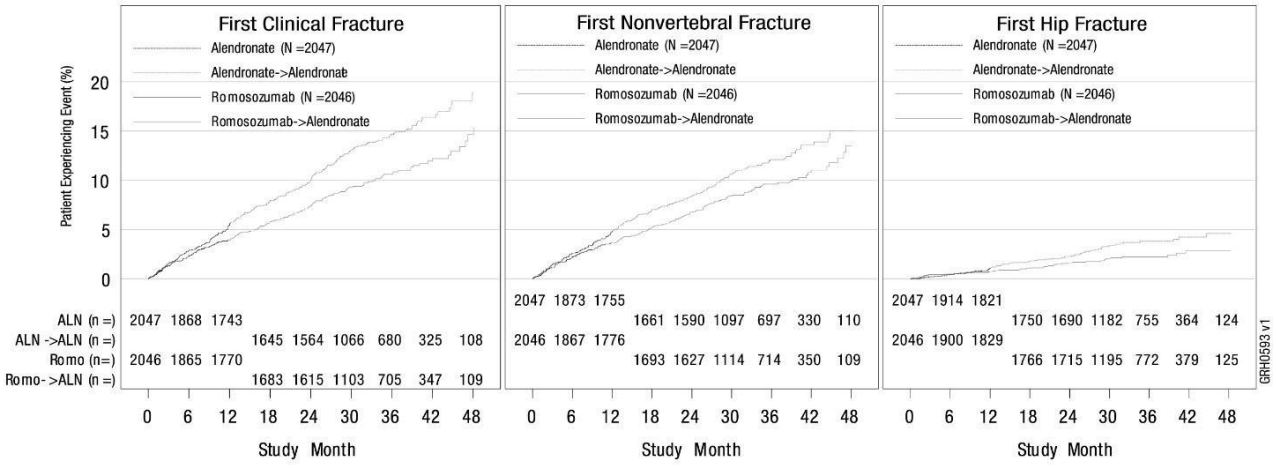
Table 3. Effect of EVENITY on the Incidence and Risk of Fractures

	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)

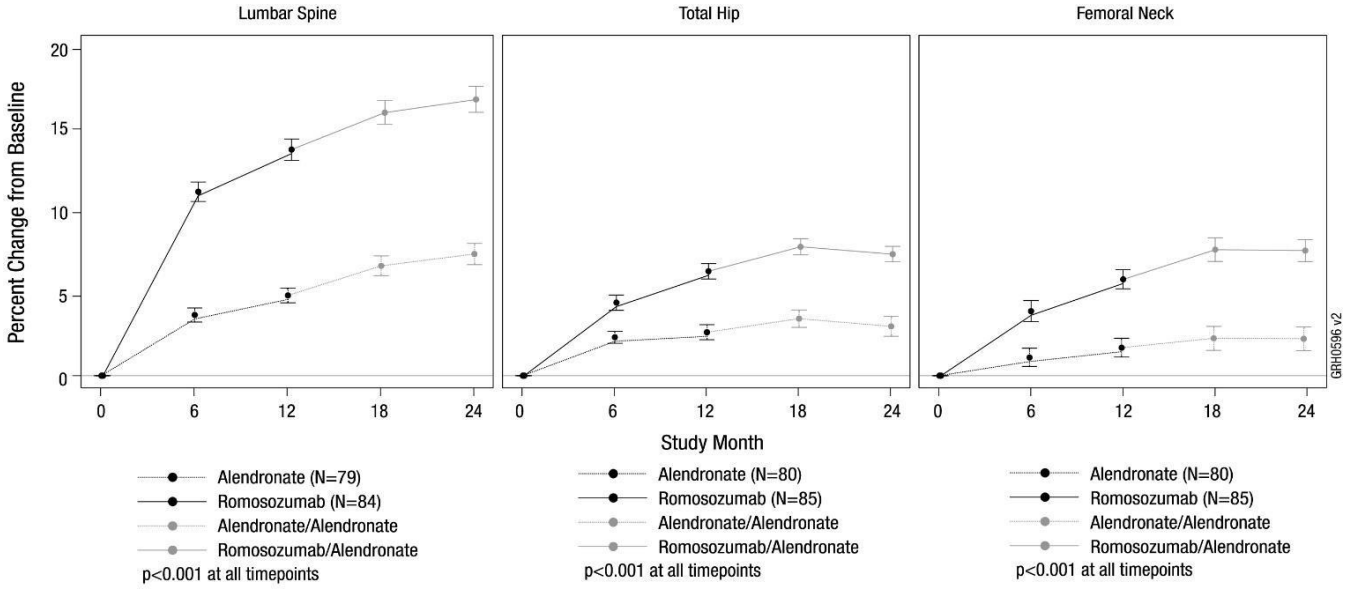
a. p-value < 0.001 based on an ANCOVA model, adjusting for treatment, age strata, presence of severe vertebral fracture at baseline, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction.

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).

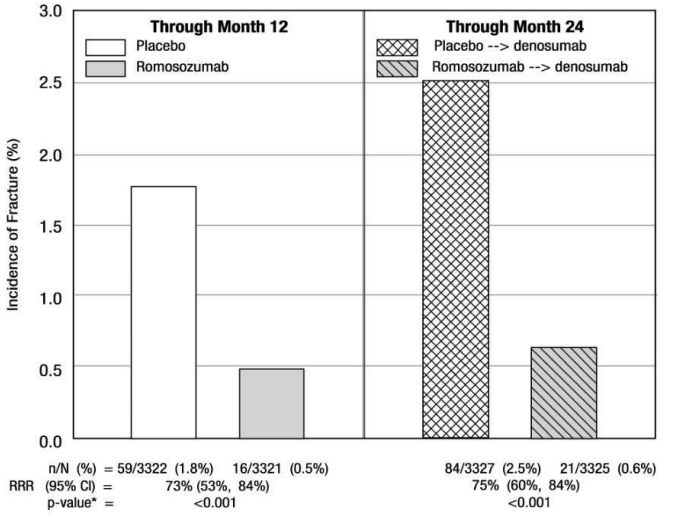
Table 5. The Effect of EVENITY on the Incidence and Risk of New Vertebral and Clinical Fractures through Month 12 and Month 24

	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.

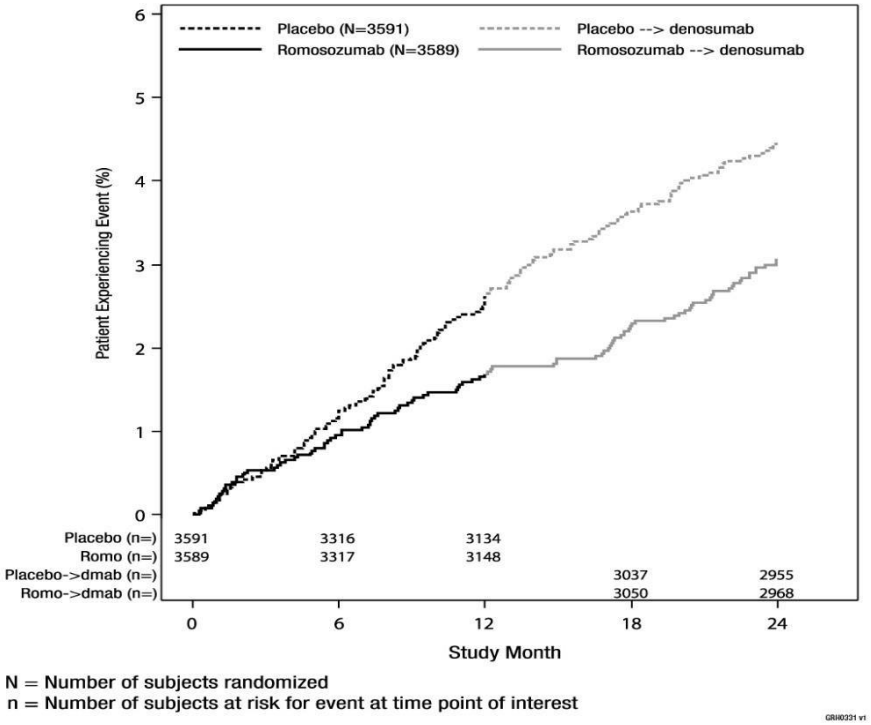
a. Absolute risk reduction is based on the Mantel-Haenszel method (new vertebral fracture) or on inverse-weighted method (clinical fracture) adjusting for age and prevalent vertebral fracture strata.
b. Relative risk reduction is based on the Mantel-Haenszel method (new vertebral fracture) or Cox proportional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

Figure 5. Cumulative Incidence of Clinical Fractures through Month 24



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]

	Proportion of Women with Fracture					
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)

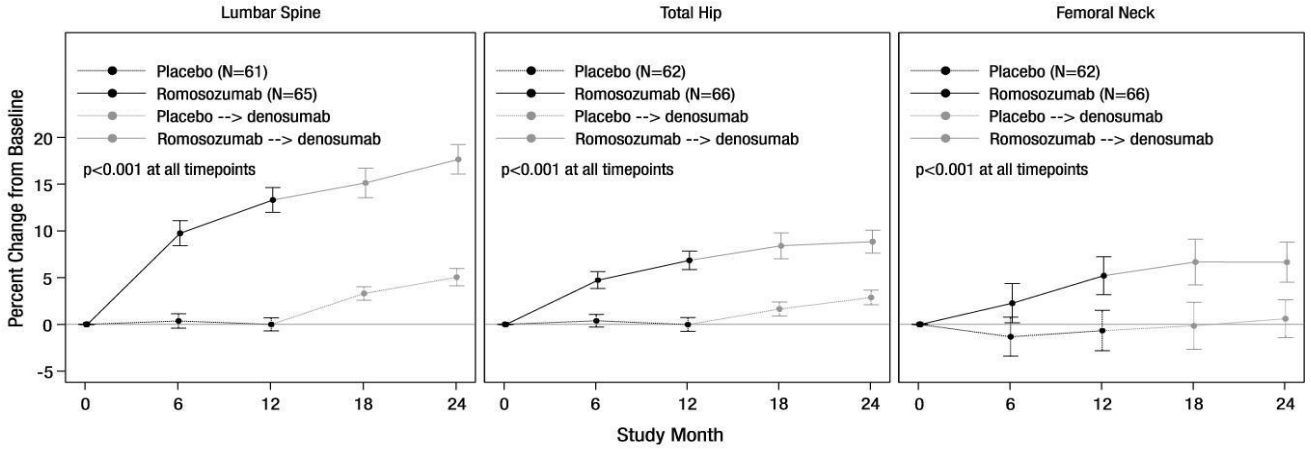
	Placebo/Denosumab Mean (95% CI) N = 3591[a]	Romosozumab/Denosumab Mean (95% CI) N = 3589[a]	Treatment Difference from placebo/Denosumab
At Month 24			
Lumbar spine	5.5 (5.3, 5.7)	16.6 (16.3, 16.8)	11.1[b] (10.8, 11.4)
Total hip	3.2 (3.1, 3.3)	8.5 (8.3, 8.7)	5.3[b] (5.1, 5.5)
Femoral neck	2.3 (2.1, 2.6)	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.

Gender:
The pharmacokinetics of romosozumab were similar in postmenopausal women and in men with osteoporosis.

Geriatrics:
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 REGISTRATION HOLDER NAME AND ADDRESS

Amgen Biopharmaceuticals Malaysia Sdn Bhd
Common Ground, 1 Powerhouse,
Horizon Penthouse, No. 1,
Persiaran Bandar Utama, Bandar Utama,
47800 Petaling Jaya, Selangor, Malaysia.

8. DATE OF REVISION OF THE TEXT

Aug 2024

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