Taiwan Food and Drug Administration

Assessment Report

Trade Name：EVENITY Solution for Injection

Active Ingredient：Romosozumab

License Number：MOHW-BI 001137

Applicant：台灣安進藥品有限公司

Approval Date：2020.07.03

Indication：
治療有高度骨折風險之停經後婦女骨質疏鬆症
EVENITY 適用於治療有高度骨折風險之停經後婦女骨質疏鬆症，其定義為發生過骨質疏鬆性骨折，或具有多重骨折風險因子。

1. Background Information

Trade Name	EVENITY Solution for Injection
Active Ingredient(s)	Romosozumab
Applicant	台灣安進藥品有限公司
Dosage Form & Strengths	注射液劑
Indication	治療有高度骨折風險之停經後婦女骨質疏鬆症 **EVENITY** 適用於治療有高度骨折風險之停經後婦女骨質疏鬆症，其定義為發生過骨質疏鬆性骨折，或具有多重骨折風險因子。
Posology	詳細內容請參閱仿單
Pharmacological Category **ATC Code**	M05BX06

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Romosozumab is a human Immunoglobulin G subclass 2 (IgG2) type antibody that could neutralize the excess sclerostin existing osteoporosis patients with high risk at fracture. Specifically, romosozumab can inhibit the interaction between the sclerostin and its endogenous receptor complex on the cell surface, and thus can promote the osteoblast-mediated bone formation. The predominant molecular mass of romosozumab determined is 148,515 Da, which is in agreement with the theoretical value (148,511 Da). Each HC contains a predominant N-linked oligosaccharide of A2G0F, attached at the consensus glycosylation site at N299.

Manufacturing

The romosozumab DS is manufactured at Immunex Rhode Island Corporation (Amgen Rhode Island (ARI)), in accordance with cGMPs. The Mfg. process of romosozumab DS consists of three key steps, including the upstream cell culture, downstream purification process and the final filtration and storage process, which had been described in sufficient detail with the accompanied process flow diagrams.

A production run begins with the WCB vial thawed, through the cell culture expansion and harvest of the production culture, followed by protein recovery and purification by a series of chromatography steps. Additional steps are introduced for inactivation and removal of

the potential viral contaminants. The DS solution is then concentrated and filtered (0.2 μm) into the 10 L storage PC container.

Controls

- The source and history of the host cell line are provided.
- The construction of expression vector and generation of the cell substrate have been described in details.
- The in-process controls, including the microbial controls, performance attributes, critical process parameters, and key process meters applied to Mfg. process are provided.
- Adventitious agents
  - No raw materials of human or animal origins are used in the romosozumab DS manufacturing processes and no concerns of TSE/BSE transmission.
  - Bacteria and fungi, mycoplasma as well as virus tests are performed on each unprocessed bulk.
  - The results of the virus clearance studies, retroviral like particles (rVLP) observed in unprocessed bulk by TEM, and the estimated safety margin retroviral contamination per clinical dose is considered acceptable.
  - Overall, the safety of romosozumab in relation to adventitious agents is considered adequate.

Process validation

The validation of the romosozumab DS Mfg. process (Process 2) was carried out on 3 consecutive lots of commercial manufacturing scale. Results obtained from these batches provide evidence that all performance parameters of romosozumab DS meet the pre-defined criteria and demonstrate the process consistency.

Manufacturing process development

During the process development course of the DS, the following process changes or improvements were implemented.

- ✓ from Process 1 (70 mg/mL) to Process 2 (the commercial process, 120 mg/mL) at ATO site
- ✓ scale-up and transfer of Process 2 from initial mfg. site (ATO, 2 kL) to the commercial mfg. site (ARI, 15 kL)

Based on the comprehensive comparability bridging studies, it was confirmed that DS manufactured by the commercial process (Process 2 (ARI)) has a highly comparable quality profile with those made by previous developmental Mfg. processes.

Characterization

The characterization included following studies：

- Biochemical studies to assess primary structure, glycosylation, disulfide structure, charge variants, and size variants;
- Biophysical studies to assess secondary structure, tertiary structure, and thermal stability;
- Biological studies to demonstrate the mechanism of action, including antigen specificity and Fc functionality;
- Forced degradation studies to assess how romosozumab responds to specific conditions to reveal potential degradation pathways under typical and atypical conditions.

DS specification

The release testing of romosozumab DS includes identity, purity/impurities, potency and contaminants. These tests are performed either according to compendial methods or by in-house analytical methods. Descriptions of the non-compendial analytical procedures validation summaries have been provided. The proposed specifications of DS are considered adequate and acceptable.

Reference materials

The qualification reports of current RSs have been provided.

Stability

The stability data from production batches made by Process 2 at ARI site were provided and the results revealed that romosozumab DS is stable under storage condition for up to 60 months, which supports the proposed shelf-life of 60 months for the DS stored at the recommended temperature of −30 ± 10°C in the proposed PC container.

2.1.2 Drug product

Romosozumab Drug Product (DP) is presented as a sterile, single-use, preservative- free solution for subcutaneous (SC) administration in a Crystal Zenith (CZ) resin prefilled syringe (PFS) with an inserted needle. The PFS contains a 1.17 mL deliverable volume of 90 mg/mL romosozumab formulated in 55 mM acetate, 13 mM calcium, 6% (w/v) sucrose, and 0.006% (w/v) polysorbate 20, pH 5.2.

Manufacturing

Romosozumab PFS DP are manufactured and released at Patheon Italia S.p.A., and then receive their DP packaging as well as the finished DP lot release at Amgen Manufacturing Ltd (AML). The Mfg. process consists of DS thawing, formulation buffer and formulated bulk preparation, as well as sterile filtration, aseptic filling and inspection.

Controls

The critical process parameters, key process parameters, in-process control tests that control the critical steps at Patheon Italia S.p.A. have been provided.

Process validation and/or evaluation

The validation of the commercial DP manufacturing Process 2 was carried out on 3 batches. Overall, the validation studies have demonstrated that the Mfg. processes of romosozumab DP at Patheon Italia S.p.A. are robust.

DP Specification

The specifications for romosozumab DP include general test (appearance, visible and sub-visible particles), identity, quantity, purity/impurities, size and charge variants, endotoxins, sterility and potency.

Batch analysis data of finished product batches which derived from DS produced by Process 1 (ATO, 2 kL) through Process 2 (ARI, 15 kL) are provided. The results demonstrate a satisfactory batch to batch consistency.

Reference materials

The reference standards used in the testing and release of romosozumab DP was the same as the one used for the testing and release of romosozumab DS.

Stability of the DP

The long-term and accelerated/stress stability data for DP using Process 2 DS materials are provided. The photo stability and Freeze/Thaw studies were performed on DP batches. Overall, the stability data provided could support the proposed shelf-life of 36 months when the DP is stored at the recommend condition (5°C) and the secondary packaging carton could provide adequate protection from light. In addition, stability data support short-term room temperature exposure (controlled, 25°C or less) for up to 30 days within the 36 months shelf life.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In vitro pharmacology studies showed that romosozumab bound to human, cynomolgus monkey, and rat sclerostin with high affinity. Romosozumab could block the binding of sclerostin to the ECDs of the key Wnt signaling co-receptors, LRP5 and LRP6, and block sclerostin's inhibitory effect on mineralization. In the *in vivo* ovariectomized model, compared with the control group, the r13C7 treatment increased the bone mass and bone strength throughout the dosing

period. Switching of Scl-Ab to vehicle resulted in the loss of bone mass and strength over time, but administering the RANKL inhibitor OPG-Fc or reduced-dosing frequency of r13c7 prevented these effects. Treatment with r13C7 significantly increased the gene expression of Wnt inhibitors (sost, dkk1, mepe, and dmp1). Injection of romosozumab to the aged bone-depleted OVX cynomolgus monkeys for 52 weeks resulted in rapid and marked dose-dependent increases in cortical and cancellous bone mass with normal matrix mineralization, improved cancellous bone microstructure, and enhanced bone geometry. In an osteopenic OVX rat study, pre- or co-treatment with alendronate did not affect the r13c7-increased bone formation, bone mass, and bone strength. Besides, r13c7 re-treatment robustly increased bone formation and bone mineral density (BMD) and decreased bone resorption in OVX rats. Re-treatment of r13c7 did not further increase BMD when the initial treatment period treated with OPG-Fc. Romosozumab increased wall thickness in bone multicellular units and decreased final resorption depth, yielding a positive bone balance in remodeling sites in monkey vertebra. In the secondary pharmacodynamics, r13c7 presented to improve femur fracture repair. Besides, r13c7 enhanced subchondral sclerosis but did not increase the severity of medial meniscal tear induced osteoarthritis in rats. Several studies of sclerostin with cardiovascular disease were evaluated; however, no evidence of available non-clinical data indicate a mechanistic association between sclerostin inhibition and atherosclerosis promotion.

2.2.2 Toxicological Studies

In repeated-dose toxicity studies, romosozumab treatment was generally well tolerated with minimal inflammatory infiltrates at injection sites in rats and monkeys. Romosozumab-related effects observed in the rats and monkeys were either a direct or indirect consequence of the pharmacological effects on bone. As a consequence of the increased bone formation, the bone marrow space was reduced, leading to impaired erythropoiesis. The increased bone formation did not cause any adverse clinical consequences, such as neurological or locomotor effects in rats or monkeys. Furthermore, no mineralization in tissues outside bone was observed. There were no romosozumab-related effects on fertility parameters. In a pivotal EFD study and in a combined fertility and EFD study, the reduced ventral processes on the 6th cervical vertebrae were observed at the high dose. This skeletal variation is considered a developmental delay. This anatomical structure is not present in humans, and the finding is not considered clinically relevant. In the pre- and post-natal development study, there were no romosozumab-related microscopic changes in the right femur or any skeletal abnormalities in the C6 cervical vertebrae in F1 generation pups. No neoplastic

changes were attributed to romosozumab. In local tolerance, granulomatous inflammation with proteinaceous foreign material extended peripherally from the injection site. Mononuclear infiltrates in the injection region. The lower incidence of anti-drug antibodies in romosozumab treated in monkeys. No unexpected tissue binding or cross-reactivity was observed. Romosozumab does not rely on Fc-mediated effector function, including antibody-dependent cell-mediated cytotoxicity, antibody-dependent cell-mediated phagocytosis, or complement-dependent cytotoxicity.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The active ingredient of EVENITY was romosozumab, a humanized IgG2 monoclonal antibody, which can inhibit the action of sclerostin, increase bone formation and decrease bone resorption. The dosing regimen was 210 mg subcutaneously (SC) once every month for 12 doses in the abdomen, thigh, or upper arm.

After single dose to both healthy subject and postmenopausal woman with low bone mass, the maximum serum concentration was reached about 5 days. Steady-state concentrations were achieved by month 3 following the monthly administration of 210 mg to postmenopausal women. Comparing the exposure from SC dose to that from corresponding intravenous (IV) dose, the ratio was about 0.5 and 0.7. Over the dose range of 0.1 to 10 mg/kg, romosozumab exhibited nonlinear pharmacokinetics with exposure increasing greater than dose proportionally. Also, the clearance of romosozumab decreased as the dose increased. The estimated volume of distribution at steady-state is approximately 3.92 L. The metabolic pathway of romosozumab was not clear, but it is expected to be degraded into small peptides and amino acids via catabolic pathways. The mean effective $T_{1/2}$ was 12.8 days after 3 doses of 3 mg/kg every 4 weeks. The presence of neutralizing antibodies (NAb) caused the concentration of romosozumab to decrease; however, the effect of Nab on efficacy and safety seemed to have no relationship (please referred to clinical section).

2.3.2 Interaction Studies

Because romosozumab is a monoclonal antibody, the DDI with CYP enzyme and transporters are not expected.

2.3.3 Special Populations

Romosozumab does not to adjust dose based on age, gender and disease state (low bone mass or osteoporosis). Renal impairment patients are not required to adjust dose, but incidence of hypocalcemia was higher in patients with severe renal impairment or receiving dialysis, comparing healthy subjects in the dedicated trial duration. No clinical studies have been conducted to evaluate the effect of hepatic impairment.

Finally, the pharmacokinetic studies met the minimum requirements to support the marketing authorization of EVENITY. It is recommended to approve the NDA of EVENITY from the PK/PD perspective.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, two Phase III pivotal studies are provided to support efficacy and safety of Evenity for the claimed indication. The key efficacy results of these two studies are summarized below.

- ***Study [20070337]***

Study [20070337] was a Phase III, randomized, double-blind, multi-national, multi-center, placebo-controlled study of Evenity in postmenopausal women with osteoporosis.

For the co-primary efficacy endpoints, subject incidence of new vertebral fracture at Months 12 and 24, romosozumab 210 mg QM significantly reduced the risk of new vertebral fractures compared with placebo through Month 12 (odds ratio = 0.27, 95% CI: [0.16, 0.47]; $p < 0.001$). For subjects initially randomized to romosozumab, a significant reduction in the risk of new vertebral fracture persisted through Month 24 after both groups transitioned to denosumab in the 2nd year of the study (odds ratio = 0.24, 95% CI: [0.15, 0.39]; $p < 0.001$).

Results for the key secondary fracture endpoints included in the sequential testing procedure are summarized in Table 2.4.1-1. The statistically significant results are only observed for the endpoint of the clinical fracture through Month 12.

Table 2.4.1-1 Summary of key secondary efficacy endpoints

Endpoints	Incidence (n/N1)		Absolute risk reduction (95% CI)	HR (95% CI)	Nominal p-value	significant
	Placebo	romosozumab				
Clinical fracture through Month 12	90/3591 (2.5%)	58/3589 (1.6%)	1.2% (0.4, 1.9)	0.64 (0.46, 0.89)	0.008	Yes
Non-vertebral fracture through						No
Month 12	75/3591 (2.1%)	56/3589 (1.6%)	0.8% (0.1, 1.4)	0.75 (0.46, 0.89)	0.096	
Month 24	129/3591 (3.6%)	96/3589 (2.7%)	1.0% (0.2, 1.9)	0.75 (0.52, 0.87)	0.029	
Clinical fracture through Month 24	147/3591 (4.1%)	99/3589 (2.8%)	1.4% (0.5, 2.4)	0.67 (0.52, 0.87)	0.002	NA
Major non-vertebral through						NA
Month 12	55/3591 (1.5%)	37/3589 (1.0%)	0.6% (0.1, 1.2)	0.67 (0.44, 1.02)	0.060	
Month 24	101/3591 (2.8%)	67/3589 (1.9%)	1.1% (0.3, 1.8)	0.67 (0.49, 0.91)	0.009	
New or worsening vertebral through						NA
Month 12	59/3322 (1.8%)	17/3321 (0.5%)	1.26% (0.76, 1.77)	0.29 (0.17, 0.49)	< 0.001	
Month 24	84/3327 (2.5%)	22/3325 (0.7%)	1.86% (1.27, 2.46)	0.26 (0.16, 0.42)	< 0.001	
Hip fracture through						NA

Month 12	13/3591 (0.4%)	7/3589 (0.2%)	0.3% (0.0, 0.6)	0.54 (0.22, 1.35)	0.18	
Month 24	22/3591 (0.6%)	11/3589 (0.3%)	0.4% (0.0, 0.7)	0.50 (0.24, 1.04)	0.059	

- ***Study [20110142]***

Study [20110142] was a Phase III, randomized, double-blind, multi-national, multi-center, alendronate-controlled study of Evenity in postmenopausal women with osteoporosis.

For one of primary efficacy endpoints, subject incidence of new vertebral fracture through Month 24, romosozumab 210 mg QM for 12 months followed by alendronate 70 mg QM for 12 months significantly reduced the risk of new vertebral fractures compared with alendronate alone (odds ratio = 0.48, 95% CI: [0.36, 0.64]; $p < 0.001$). For the other primary efficacy endpoint of clinical fracture, romosozumab 210 mg QM for 12 months followed by alendronate 70 mg QM through the primary analysis period significantly reduced the risk of clinical fractures compared with alendronate alone (hazard ratio = 0.73, 95% CI: [0.61, 0.88]; $p < 0.001$).

The BMD endpoints were multiplicity adjusted at Month 24 and Month 12 and included in the testing procedures. At Month 12, romosozumab significantly increased BMD compared with alendronate at the lumbar spine, total hip and femoral neck, with LS mean differences of 8.7%, 3.3%, and 3.2%, respectively (p-value < 0.001 for all 3 sites). At Month 24, romosozumab significantly increased BMD compared with alendronate at the lumbar spine, total hip and femoral neck, with LS mean differences of 8.1%, 3.8%, and 3.8%, respectively (p-value < 0.001 for all 3 sites).

The following key secondary efficacy endpoint was an interim analysis of non-vertebral fracture. The results shows that romosozumab 210 mg QM for 12 months followed by alendronate 70 mg QM for 12 months significantly reduced the risk of non-vertebral fractures compared with alendronate alone (HR = 0.81, 1-sided p-value = 0.019 < boundary of 0.0223).

In conclusion, results from the two pivotal studies are sufficient to support the efficacy of Evenity injection for the treatment of osteoporosis in post-menopausal women at high risk for fracture.

2.4.2 Safety Results

Major safety concerns are MACE (CV events), hypersensitivity, hypocalcemia, osteonecrosis of the jaw, atypical subtrochanteric and diaphyseal femoral fractures.

2.5 Bridging Study Evaluation

The exposure (C_{max} and AUC) in Japanese woman was lower than that in non-Japanese woman when dosing by body weight (mg/kg); however, the situation was reversed when dosing by fixed dose. The peak concentration (Day 1+1 week; Day 8) in Japanese woman was higher than that in global woman in three fixed dose (70mg, 140 mg and 210 mg) groups, and C_{trough} also showed same trend in different time at 210 mg dose group. This difference may be caused by body weight differences. Besides, the population PK predicted that woman in different race had similar predicted AUC_{ss}. Overall, the aforementioned difference was not significant, thus, the ethnic difference may be negligible from PK point of view.

Subgroup analyses of 998 East Asian subjects in the two pivotal studies (11,273 global subjects) of the romosozumab for the treatment of osteoporosis in postmenopausal women showed no clinically significant inter-ethnic difference in pharmacokinetics, pharmacodynamics, efficacy, and safety between the East Asian and the global subjects.

2.6 Conclusion

The submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. The efficacy was demonstrated in two pivotal studies. The most important safety concern is CV risk. The sponsor narrowed the claimed indication to high risk group or 2nd line therapy, along with label warning of not using Evenity in patients with recent MI or stroke; however, 2nd line population was not included in the two pivotal studies hence their efficacy is uncertain. Hence, the approved indication of Evenity should be revised as the following.

「Treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture.」

3. Post-Marketing Requirements

(1) Post-marketing studies for CV risks
(2) Routine pharmacovigilance
(3) Suggests PK study in patients with hepatic impairment.