CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761062Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761062
PDUFA Goal Date	April 9, 2019
OSE RCM #	2018-1473
Reviewer Name	Jacqueline Sheppard, PharmD
Team Leader	Laura Zendel, PharmD
Deputy Division Director	Jamie Wilkins, PharmD
Review Completion Date	March 29, 2019
Subject	Evaluation of Need for a REMS
Established Name	romosozumab
Trade Name	Evenity
Name of Applicant	Amgen, Inc.
Therapeutic Class	Sclerostin inhibitor
Formulation	Prefilled syringe (PFS), (b) (4)
Dosing Regimen	2 injections (210 mg) subcutaneously once a month for 12 months

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1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) romosozumab (BLA 761062) is necessary to ensure the benefits of this product outweigh its risks. Amgen Inc. originally submitted romosozumab for the treatment of osteoporosis in postmenopausal women at high risk of fracture or patients who have failed or are intolerant to other available osteoporosis therapy on July 19, 2016. The application received a Complete Response (CR) on July 13, 2017 due to a potential cardiovascular safety signal detected toward the end of the review cycle. The Application was discussed at a meeting of the Bone, Reproductive, and Urologic Drugs Advisory Committee on January 16, 2019.

The original DRISK review[1] concluded that in the absence of a full analysis of the safety profile, risk management recommendations were unable to be determined. The current resubmission, dated July 9, 2018, includes a comprehensive reanalysis of the cardiovascular findings from pivotal phase 3 studies.

DRISK and the Division of Bone, Reproductive, and Urologic Products (DBRUP) agree that a REMS is not necessary to ensure the benefits of romosozumab outweigh its risks. Romosozumab shows substantial increases in bone mineral density (BMD) and antifracture efficacy for vertebral and nonvertebral fractures. While the increased rate of cardiac incidences in one of the pivotal trials is concerning, the interpretation of the potential cardiovascular signal has yet to be fully determined. In the Agency's experience, REMS programs have minimal impact in mitigating the risk of MACE unless the REMS is designed specifically to limit who might receive the product. It is important to keep in mind that such a REMS may not have the intended impact and is likely to require elements which could be burdensome to healthcare providers and patients. Therefore, as this product is efficacious and will be used in a higher risk population, a REMS is not necessary and the risks of this product will be communicated through labeling including a boxed warning, limitations of use, and a Medication Guide.

2 Background

2.1 PRODUCT INFORMATION

Romosozumab, a new molecular entity, is a humanized immunoglobulin (IgG2) monoclonal antibody proposed for the treatment of osteoporosis in postmenopausal women at high risk of fracture or patients who have failed or are intolerant to other available osteoporosis therapy. The proposed dose is 210 mg given subcutaneously (SQ) once a month over a 12 - month period in a physician's office. Romosozumab was approved in Japan on January 8, 2019.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761062 relevant to this review:

- **07/16/2016:** The Agency received BLA 761062 for the treatment of osteoporosis in post-menopausal women at increased risk of fracture.
- **07/13/2017:** The Agency issued a Complete Response (CR) due to a new safety signal showing a higher incidence of cardiovascular serious adverse events with romosozumab.

- **10/26/2017:** The Agency held a Type A End of Review Meeting with Amgen to discuss the Applicant's plan to address the numerical imbalance in cardiovascular adverse events and the characterization of the cardiovascular safety of romosozumab in the BLA resubmission.
- **07/09/2018:** The Agency received the Class 2 resubmission of BLA 761062 for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.
- **01/08/2019:** The Agency issued a major amendment extending the review clock for three months due to the pending Advisory Committee meeting and outstanding information requests concerning the cardiovascular risks of Romosozumab.
- **01/16/2019:** The Bone, Reproductive, and Urologic Drugs Advisory Committee was convened to discuss the potential cardiovascular risks associated with romosozumab and the design of any post-marketing studies. The Advisory Committee concluded that the risks of Romosozumab could be managed with labeling and post-marketing studies.
- **01/30/2019:** The Agency held a Post-Advisory Committee Debrief with Amgen via teleconference to discuss the labeling and post-marketing safety study recommendations proposed by the Advisory Committee.

3 Benefit Assessment

The efficacy of romosozumab is derived from two pivotal fracture studies, Study 2007337 (Study 337)[a] and study 20110142 (Study 142). For additional details regarding the development program, see the DRISK review dated July 13, 2017[2], DBRUP Clinical Reviews[3,4] dated May 3, 2017 and June 13, 2017, and the Cross-Disciplinary Team Leader (CDTL) Review[5] dated June 13, 2017. As Study 337 was discussed in the previous review, the remainder of this section will focus on Study 142[b].

Study 142 (N = 4093) is a phase 3, randomized, double-blind, alendronate-controlled study designed to demonstrate that treatment with romosozumab 210 mg SC monthly for a duration of 12 months followed by alendronate 70 mg weekly is safe and superior in efficacy in comparison to alendronate 70 mg weekly alone in women with post-menopausal osteoporosis. The two primary endpoints were 1) the subject incidence of clinical fracture (nonvertebral and clinical vertebral fracture) through the primary analysis period and 2) the subject incidence of new vertebral fracture through month 24. At 24 months, the subject incidence of new vertebral fracture with romosozumab followed by alendronate was 4.1% compared to 8.0% with alendronate alone, with a significant relative risk reduction (RRR) of 50% (95% CI: 34, 62; $p < 0.001$). At the end of the primary analysis period, the subject incidence of clinical fracture with romosozumab followed by alendronate was 9.7% compared to 13.0% with alendronate alone, with a hazard ratio of 0.73 (95% CI: 0.61, 0.88; $p < 0.001$). Romosozumab also significantly increased bone

[a] Reviewed with the original BLA submission

[b] Data from this study became available late in the original cycle of the BLA and was not analyzed in the previous review.

mineral density (BMD) at all sites. At month 12, compared with control, romosozumab increased BMD by 12.7% at the lumbar spine, 5.8% at the total hip, and 5.2% at the femoral neck. The clinical reviewer[6] states that the additional efficacy data from Study 142 strengthens the previous assessment of clinical benefit as established in the original BLA with Study 337.

4 Risk Assessment and Safe Use Conditions

The safety profile of romosozumab (with the notable exception of the cardiovascular risk) is well-characterized in the original BLA submission. Previously identified risks of romosozumab include hypersensitivity, injection site reactions, hypocalcemia, osteonecrosis of the jaw, and atypical femoral fractures and are discussed in the DRISK review dated July 13, 2017.

4.1 MAJOR ADVERSE CARDIAC EVENTS (MACE)

Across the pivotal phase 3 studies, the incidence of major adverse cardiac event (MACE)[c] during the 12-month double-blind period was 1.3% in the romosozumab group and 0.9% in the control group[d] (HR 1.4). This is driven by an imbalance of cardiovascular events in Study 142. Study 142 had a higher subject incidence of positively adjudicated myocardial infarction (MI) (16 [0.8%] vs. 5 [0.2%]) and stroke (13 [0.6%] vs. 7 [0.3%]) in the romosozumab group when compared with alendronate during the 12-month double-blind period. These events occurred in patients with and without history of MI or stroke. Cardiovascular death occurred in 17 women (0.8%) in the Romosozumab group vs. 12 (0.6%) in the control group. In contrast, these events are balanced in the romosozumab and placebo groups in the larger Study 337 where cardiovascular death occurred in 17 women (0.5%) in the romosozumab group vs 15 women (0.4%) in the control group and the rates of MI and stroke were (9 [0.3%] vs. 8 [0.2%]) and (8 [0.2%] vs. 15 [0.4%]) respectively.

Given the differences in cardiovascular safety results between the trials, it is unclear if the cardiovascular safety signal reflects a true increase in cardiovascular risk with romosozumab therapy. The Division of Cardiovascular and Renal Products (DCRP) was consulted by the clinical review team and analyzed the cardiovascular safety signal from the meta-analysis of the pivotal trial and determined the adjudication processes were adequate. DCRP concluded that the overall hazard ratio for the cardiovascular events was low but there was a marginally significant hazard ratio for romosozumab versus the comparator. The final clinical analysis of the data states several factors that make the interpretation of the cardiovascular signal difficult: 1) The pivotal studies were not designed to assess cardiovascular safety outcomes 2) Currently available nonclinical and human genetic data do not

[c] MACE is defined as a composite endpoint of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke

[d] Control group is compromised of both alendronate and placebo.

provide evidence of a biological mechanistic cause of cardiovascular events with romosozumab 3) There may be an alternative explanation for the observed imbalance in Study 142, such as a cardioprotective effect of alendronate and 4) The number of cardiovascular events in both studies were low and may not be outside the range of expectation for the study population.

5 Risk Management Activities Proposed by the Applicant

In addition to routine pharmacovigilance and labeling, the applicant proposed enhanced pharmacovigilance during the post-marketing period to assess the frequency of cardiovascular events and further characterize the cardiovascular risks associated with romosozumab. Additionally, a post-marketing observational study will be required to assess the frequency of serious cardiovascular events in real-world conditions.

Reviewer's Comments: *We note that these activities proposed by the applicant are outside of the scope of a REMS and defer to the Division of Pharmacovigilance and Division of Epidemiology for review and input.*

6 Discussion of Need for a REMS

Romosozumab is proposed for the treatment of osteoporosis in postmenopausal women at high risk of fracture or patients who have failed or are intolerant to other available osteoporosis therapy. The clinical efficacy trials for romosozumab showed benefit with substantial increases in bone mineral density (BMD) and antifracture efficacy for vertebral and nonvertebral fractures. As the efficacy and non-cardiovascular safety profile were discussed in the previous submission, the benefit risk analysis in this review will primarily focus on the better defined cardiovascular risk contained in the resubmission.

Romosozumab is associated with a greater incidence of MACE (1.3%) compared to the control group (0.9%) across the pivotal phase 3 studies. This imbalance is seen as an increase in the incidence of MI and stroke in Study 142. Because of the MACE events in Study 142, and the subsequent potential cardiovascular signal, the Agency must weigh the risks of potential cardiovascular events (specifically MI and stroke) with the benefit of approving romosozumab.

Furthermore, there is uncertainty about the cardiovascular signal seen in romosozumab. While the increased incidence of cardiovascular events is evident in Study 142, the interpretation of the cardiovascular signal has yet to be fully determined. According to the clinical review team, several factors make the interpretation of the cardiovascular signal difficult: 1) The pivotal studies were not designed to assess cardiovascular safety outcomes 2) Currently available nonclinical and human genetic data do not provide evidence of a biological mechanistic cause of cardiovascular events with romosozumab 3) There may be an alternative explanation for the observed imbalance in Study 142 such as a cardioprotective effect of alendronate and 4) The numbers of events that drove the events are very low and may have occurred because it was in the range of expectation of the study population.

The Application was discussed at a meeting of the Bone, Reproductive, and Urologic Drugs Advisory Committee on January 16, 2019. The Advisory Committee concluded that the overall benefit/risk profile of Romosozumab was acceptable to support approval and the cardiovascular risks of romosozumab could be managed with labeling and post-marketing studies.

The Agency's approach is generally to consider whether the risks for a product can be adequately communicated with labeling including a boxed warning, concise indications, and a Medication Guide for patients. A REMS might be considered, if it can reasonably mitigate the risk and ensure the benefits of the drug outweigh its risk. In the Agency's experience, REMS programs have minimal impact in mitigating the risk of MACE unless the REMS is designed specifically to limit who might receive the product. It is important to keep in mind that such a REMS may not have the intended impact and is likely to require elements which could be burdensome to healthcare providers and patients.

DRISK and DBRUP concur that a REMS is not necessary to ensure the benefits outweigh the risks of romosozumab. Serious cardiovascular events of MI and stroke are an important potential risk and will require clear risk communication in labeling. Therefore, as this product is efficacious and will be used in a higher risk population, a REMS is not necessary. Risk minimization will include communication of important risks for romosozumab through labeling including a boxed warning, limitations of use, warning and precaution statements alerting patients and prescribers to monitor for symptoms of MI and stroke during treatment and a Medication Guide.

Conclusion & Recommendations

Based on the available data, risk mitigation measures beyond professional labeling are not warranted for romosozumab and a REMS is not necessary to ensure the benefits outweigh the risks. Romosozumab shows substantial increases in bone mineral density (BMD) and antifracture efficacy for vertebral and nonvertebral fractures. While the increased rate of cardiac incidences in one of the pivotal trials is concerning, the interpretation of the potential cardiovascular signal has yet to be fully determined.

Should Division of Bone, Reproduction, and Urologic Products have any concerns or questions, or feel that REMS is warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

8 Appendices

8.1 REFERENCES

[1] Joshi A. Division of Risk Management. DRISK Review for Romosozumab [BLA 761062], dated July 13, 2017

[2] Joshi A. Division of Risk Management. DRISK Review for Romosozumab [BLA 761062], dated July 13, 2017

[3] Chang D. Division of Bone, Reproductive and Urologic Products. Clinical review for Romosozumab [BLA 761062], dated May 3, 2017.

[4] Chang D. Division of Bone, Reproductive and Urologic Products. Clinical review Update and Addendum for Romosozumab [BLA 761062], dated June 13, 2017

[5] Kehoe T. Division of Bone, Reproductive and Urologic Products. CDTL review for Romosozumab [BLA 761062], dated June 13, 2017

[6] Karp J. Division of Bone, Reproductive and Urologic Products. DRAFT Uni-review for Romosozumab [BLA 761062], dated March 6, 2019

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Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Application Type	BLA
Application Number	761062
PDUFA Goal Date	7/19/2017
OSE RCM #	**2016-1763**
Reviewer Name(s)	Ameet Joshi, PharmD., Division of Risk Management (DRISK)
DRISK Acting Team Leader	Leah Hart, PharmD., DRISK
Deputy Division Director	Jamie Wilkins Parker, PharmD., DRISK
Review Completion Date	July 13, 2017
Subject	Evaluation to determine if a REMS is necessary
Established Name	Romosozumab
(Proposed) Trade Name	Evenity
Applicant	Amgen, Inc.
Therapeutic Class	Immunomodulator; Sclerostin inhibitor
Formulation(s)	Prefilled syringe (PFS), (b) (4)
Dosing Regimen	2 Injections for 210 mg IM injection once a month (Total of 24 injections for 12 month treatment course)

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Executive Summary

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) (Evenity) romosozumab is necessary to ensure the benefits of this product outweigh its risks. The Applicant (Amgen Inc.) submitted a Biologic Licensing Application (BLA 761062) with the proposed indication of treating osteoporosis in post-menopausal women at an increased risk of fracture. The risks associated with romosozumab include hypersensitivity, hypocalcemia, osteonecrosis of the jaw (ONJ), atypical femoral fracture (AFF), and cardiac events. The applicant did not submit a proposed REMS with this application.

The regulatory decision regarding the need for a REMS is based on whether a REMS is necessary to ensure the benefits outweigh the risk of the drug. In the case, the analysis of the safety profile has not yet been fully determined. Therefore, at this time, a final determination has not been made regarding the potential benefits of this application, and this reviewer is not able to determine if a REMS would be needed to ensure that the benefits outweigh the risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[1] Evenity (romosozumab) is necessary to ensure the benefits of this product outweigh its risks. Amgen Inc. (Amgen) submitted a Biologic Licensing Application (BLA-761062) for romosozumab with the proposed indication for patients with postmenopausal osteoporosis at increased risk of a fracture (b) (4). This application is under review in Division of Bone, Reproductive and Urological Products (DBRUP). The applicant did not submit a REMS with this application, but proposed post market safety monitoring through clinical studies as part of their routine pharmacovigilance program, labeling, and a Medication Guide to communicate the risks.

2 Background

2.1 Product Information

Romosozumab, a new molecular entity, is a humanized immunoglobulin (IgG2) monoclonal antibody proposed for the treatment of osteoporosis in postmenopausal women at increased risk for fracture. The drug binds to and inhibits the glycoprotein sclerostin. Sclerostin negatively regulates the Wingless-related integration site (Wnt) signaling pathway. By decreasing the signaling in the osteoblast-lineage cells, the Wnt pathway inhibits bone formation and increases bone resorption normally. The inhibition of this pathway will have a dual effect of increasing bone formation and reducing bone resorption.

[1] FDAAA factor (F): Whether the drug is a new molecular entity

The proposed dose is 210 mg given subcutaneously (SQ) once a month over a 12 month period in a physician's office.[2] The proposed commercial product is a (b) (4) prefilled syringe with a concentration of (b) (4). Romosozumab is not currently approved in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for BLA 761062 relevant to this review:

- 7/19/2016: BLA 761062 submission for treatment of osteoporosis in postmenopausal women received.
- 12/13/2016: Mid cycle meeting held where DRISK recommended no REMS for this product due to awareness by the prescriber/patient population using a similar drug and risk profile. It was recommended that romosozumab risks can be communicated via labeling.
- 1/5/2017: Mid cycle communication held between the Agency and the Applicant. The Agency informed the Applicant that based on the currently available data; there are no safety issues that require risk management strategies beyond labeling for romosozumab. However, the Agency stated there may be safety concerns regarding osteonecrosis of the jaw and atypical femoral fractures that need to be addressed through labeling and a Medication Guide.
- 5/15/2017: Amgen contacted the Agency on May 15, 2017, to notify that they had completed the analysis of the preliminary, high level results for the phase 3 randomized, double-blind, active-comparator study (20110142) of romosozumab followed by alendronate compared to alendronate alone. Amgen stated that aspects of the data are unanticipated and they are currently undertaking additional evaluation. Amgen requested a meeting with the FDA to share and discuss the information
- 5/19/2017: Amgen and the Agency had a meeting to discuss the results of the phase 3 20110142 study that reported an imbalance of adjudicated serious adverse cardiovascular events in romosozumab (2.5%) treated patients versus alendronate (1.9%) patients. With two months on the review clock, the Agency stated they would not be able to take a favorable action on this review cycle and that a withdrawal or complete response action are the options remaining.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Osteoporosis is characterized by low bone mass, deterioration of bone tissue, disruption of bone architecture, compromised bone strength, and an increase in the risk of fracture. The World Health Organization defines osteoporosis as a bone mineral density (BMD) less than or equal to 2.5 standard deviations below the mean BMD of a young adult population.[3] The most damaging fractures occur from vertebral fractures, and can be associated with increased disability and mortality among the elderly. [4]

[2] FDAAA factor (D) The expected or actual duration of treatment with the drug
[3] (Amgen, 2016)
[4] FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug

The National Osteoporosis Foundation (NOF) estimates that 10.2 million Americans have osteoporosis and that an additional 43.4 million have low bone mass.[5] More than 2 million osteoporosis-related fractures occur annually in the U.S., more than 70% of these occur in women. By 2025, the costs for fractures will be estimated to be $25 billion. [6]

3.2 Description of Current Treatment Options

There are several pharmacologic treatment options available to treat osteoporosis with varying mechanisms of action. Current FDA approved options include bisphosphonates, calcitonin, estrogen agonists/antagonists or hormone therapy, estrogen complexes, parathyroid hormone, and ligand inhibitors. Of the approved biologic treatments for osteoporosis in postmenopausal women, two were approved with a REMS, Prolia (denosumab) and Forteo (teriparatide). The Prolia REMS includes a Medication Guide and a Communication Plan. The goals of the REMS are:

- Mitigate the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, serious infections, and dermatologic reactions by
    - Informing healthcare providers and patient about the risks of (1) hypocalcemia, (2) osteonecrosis of the jaw, (3) atypical femoral fractures, (4) serious infections, and (5) dermatologic reactions associated with Prolia
    - Informing healthcare providers they should counsel patients about the risks associated with Prolia.

The Forteo REMS, consisted of a Medication Guide and a Communication Plan both of which were recently released because the Communication Plan was complete and the goals were being met. The goal of the REMS was:

To mitigate the potential risk of osteosarcoma associated with Forteo by:

- Alerting and warning healthcare providers and patients about the potential risk
- Informing healthcare providers of the 2-year maximum lifetime duration of treatment with Forteo and proper patient selection
- Informing and educating healthcare providers and patients about the voluntary Forteo patient registry.

While the majority of the therapies promote bone resorption, antiresorptive therapy cannot truly restore bone structure and mass, and does not fully protect osteoporotic patients at high risk of imminent fracture. [7] There are fewer in number which promotes bone formation and resorption as romosozumab is offering. None of the pharmacologic therapies should be used indefinitely and duration decisions should be individualized based on agent and patient characteristics. See the table below for a summary of FDA approved treatment options for the treatment of post-menopausal osteoporosis in women.

[5] FDAAA factor (A): The estimated size of the population likely to use the drug involved.
[6] (American Association of Clinical Endocrinologists and American College of Endocrinology, 2016)
[7] M.S. Ominsky, et al, Effects of sclerostin antibodies in animal models of osteoporosis, Bone (2016).

Summary of FDA Approved Products for the Treatment for Osteoporosis in Postmenopausal Women

Drug Class or Established Name	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
parathyroid hormone 1–34 (teriparatide)	20 mg SC daily	Risk of osteosarcoma (do not use in patients with increased baseline risk of osteosarcoma) Must limit use to 2 years	Boxed Warning Medication Guide Communication Plan
bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid)	Alendronate: 70 mg tablet weekly or 70 mg solution weekly or 10 mg tablet daily for treatment Ibandronate: 3 mg every 3 months intravenously Zoledronic acid: 5 mg every year intravenously	All: Osteonecrosis of the jaw Alendronate: Must remain upright for 30 minutes after dosing Ibandronate: Anaphylaxis with injection Must remain upright for 60 minutes after dosing with tablet	Medication Guide
calcitonin	Injection: 100 international units per day SC or intramuscularly Nasal Spray: 200 international units per day intranasally	Nasal Spray: Nasal adverse reactions including nasal ulceration	None
estrogen agonist/ antagonist (raloxifene)	60 mg orally daily	Increased risk of venous thromboembolism and death from stroke	Boxed Warning Medication Guide
tissue-selective estrogen complex (conjugated estrogens/ bazedoxifene)	0.45 mg/20 mg orally daily	Increased risk of endometrial cancer, cardiovascular disorders, and probable dementia	Boxed Warning

receptor activator of nuclear factor kappa-B (RANK) ligand inhibitor (denosumab)	60 mg SC every 6 months	Osteonecrosis of the jaw, severe infections, dermatologic reactions, suppression of bone turnover	Medication Guide, REMS communication plan

4 Benefit Assessment

The pivotal phase 3 study (study 20070337) was conducted in 222 centers in Europe, Central/Latin America, Asia, North America and Australia/New Zealand and randomized 7180 postmenopausal women (ages 55 to < 85) to placebo (n=3591) and romosozumab (n=3589) over a 36 month treatment period. There is a 24 month primary analysis period of 12 months of double-blind romosozumab (210 mg SC monthly) or placebo followed by 12 months of denosumab 60 mg Q6 months or 12 months placebo to assess the effect of romosozumab treatment. The final 12 months is an open-label extension period in which subjects received only denosumab 60 mg Q6 months to investigate the maintenance of treatment effect through month 36, which at the time of this review is still ongoing. The primary endpoint for the study was subject incidences of new vertebral fractures through month 12 and 24. The secondary endpoints for the study include the percentage change in bone mineral density (BMD) in the lumbar spine, hip, and femoral neck.[8] Additional safety and supportive efficacy studies include the phase 2a dose ranging study in postmenopausal women with low BMD (20060326), phase 2b dose-ranging study in postmenopausal Japanese women with osteoporosis (20101291), phase 3 placebo-controlled non-inferiority study (20120156), and a phase 3b teriparatide-controlled study in postmenopausal women transitioning from oral bisphosphonates to romosozumab or teriparatide (20080289).

The pivotal phase 3 study (20070337) shows romosozumab significantly reduced new incident vertebral fractures compared with placebo through the first year by a 73% risk reduction (fracture rate: 0.5% v. 1.8%, $p < 0.001$) and persisted once patients switched to denosumab until month 24 (fracture rate: 0.6% v. 2.5%, $p < 0.001$) with a 75% risk reduction. For non-vertebral fractures, the relative risk reduction for non-vertebral fractures through month 12 in comparison to placebo (fracture rate: 1.6% v. 2.1%, p=0.096) and through month 24 (fracture rate: 2.7% v. 3.6% p=0.057) did not meet statistical significance. The incidence of clinical fractures with romosozumab was reduced by 36% in comparison to placebo (fracture rate: 1.6% v. 2.5%, p=0.008) in the first 12 months and persisted through month 24 (fracture rate: 2.8% v. 4.1%, p=0.096) but not statistically significant after a transition to denosumab therapy from month 12 to 24.

The secondary endpoint for bone mineral density showed a statistically significant increase from baseline to month 12 in 98.9% (p<0.0001), 94.1% (p<0.0001), and 90% respectively (p<0.0001) at lumbar

[8] T, D Chang. Summary Review for Romosozumab (BLA761062) May 3, 2017

spine, total hip, and femoral neck areas. By comparison, the placebo group where 12 months of placebo followed by denosumab reported 53%, 52.5%, and 51.9% increases respectively.

The bone mineral density percent increase from baseline was greater in the romosozumab/denosumab group in comparison to the placebo/denosumab therapy group.

The clinical reviewer concluded that romosozumab is effective to reduce the risk of vertebral fractures in postmenopausal women and has qualities of bone formation and antiabsorption of bone.[9]

5 Risk Assessment and Safe-Use Conditions

The safety information for romosozumab was comprised primarily from the 12 month placebo controlled postmenopausal osteoporosis (PMO) safety analysis set. The safety population included 8274 postmenopausal women in phase 2 and 3 studies; 7157 of which came from the phase 3 study (20070337). The additional subjects were from the phase 2 and non-pivotal phase 3 studies. All of the patients received at least one dose of romosozumab or placebo.

The most commonly occurring adverse events associated with romosozumab were nasopharyngitis (13.2% romosozumab, 12.3% placebo), arthralgia (romosozumab 12.7%, 11.8% placebo) and back pain (romosozumab 10.3%, placebo 10.5%) with similar incident rates between both treatment and placebo groups.

5.1 Serious Adverse Events (SAE)

Serious adverse events potentially causally related to romozosumab use are osteonecrosis of the jaw, atypical femoral fractures, hypersensitivity, and cardiovascular events.[10]

5.1.1 Deaths

There were a total of 53 deaths (0.7%), with 29 deaths in the placebo and 24 deaths in the treatment group. The most common reason for death was not otherwise specified (n=5). There was an imbalance of lung carcinoma, however these cases (n=4) all occurred in former smokers, or in patients with a familial or personal history of cancer. The six causes of death in the pivotal trial that were cardiac related (congestive cardiomyopathy, DVT, cardiac arrest, cardiac failure congestive et al) at the time of this review do not have information to confirm or refute that the fatal cardiac events were attributed to the drug. [i] The other causes of death all occurred in single patients, and were, in the opinion of the clinical reviewer, not drug related.

5.1.2 Cardiovascular Events

[9] FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.
[10] FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug

New, unexpected safety findings from Study 20110142 and Study 20110174 (the phase 3 randomized, double-blind, active-comparator study of romosozumab followed by alendronate compared to alendronate alone) identify an imbalance of incidences of cardiovascular events, with higher incidences in the romosozumab group when compared to placebo. Final analyses of these studies are yet to be completed, as the studies ended in April, 2017.[11] In light of this new information the clinical reviewer is recommending a complete response (CR) for this review cycle. Numerical data are presented below in Table 1:

Table 1: Positively Adjudicated CV Events in Study 20110142:

Category	12-Month Double-blind Period		Primary Analysis Period	
	Aln (N = 2014) n (%)	Romo (N = 2040) n (%)	Aln/Aln (N = 2014) n (%)	Romo/ Aln (N = 2040) n (%)
Number of subjects reporting treatment-emergent adjudicated positive cardiovascular serious adverse event	38 (1.9)	50 (2.5)	122 (6.1)	133 (6.5)
Cardiac ischemic event	6 (0.3)	16 (0.8)	20 (1.0)	30 (1.5)
Cerebrovascular Event	7 (0.3)	16 (0.8)	27 (1.3)	45 (2.2)
Heart Failure	8 (0.4)	4 (0.2)	23 (1.1)	12 (0.6)
Death (CV related and unclassified)	12 (0.6)	17 (0.8)	55 (2.7)	58 (2.8)
Non-coronary Revascularization	5 (0.2)	3 (0.1)	10 (0.5)	6 (0.3)
Peripheral Vascular Ischemic Event not Requiring Revascularization	2 (<0.1)	0 (0.0)	5 (0.2)	2 (<0.1)

Aln= alendronate; Romo= romosozumab
*Death events include fatal adverse events adjudicated as cardiovascular-related or undetermined to be cardiovascular
Source: Amgen presentation May 19, 2017 meeting(slide 16)

5.1.3 Hypersensitivity

In the safety analysis set of 12 month placebo controlled population (20070337, 20060326, 20101291) 7% of the romosozumab group and 7% of the placebo group experienced hypersensitivity. The most common events were rash, allergic dermatitis, and eczema. Although one death was detected during the MedDRA Standardized Query search for terms to detect hypersensitivity, in this instance, circulatory collapse, it occurred in a patient whose last dose of product was 9 days prior (event occurred on day 345), and did not experience any flushing, pruritus, or urticarial preceding the event. Of note, these hypersensitivity reactions occurred with a 70 mg/mL drug concentration; the to-be-marketed formulation will be 90 mg/mL. A late trial which evaluated the 90 mg/mL formulation (Study 20120156 which evaluated BMD changes in patients taking the 70 mg/mL formulation vs. the 90 mg/mL formulation) demonstrated a rate of 11% hypersensitivity in the 90 mg/mL romosozumab group

[11] TD Chang, Clinical Review Update and Addendum, [BLA761062] June 13, 2017

compared to a rate of 3% in the 70 mg/mL study group. Therefore, although the pooled safety population did not demonstrate an imbalance in hypersensitivity reactions, the higher, to-be-marketed concentration did demonstrate a potential imbalance in these reactions, and will therefore be labeled with a warning.

5.1.4 Osteonecrosis of the Jaw

Romosozumab's effect of antiresorptive activity increases the risk for osteonecrosis of the jaw (ONJ). There was one adjudicated case of ONJ documented in the pivotal 12 month placebo controlled population (with the exception of Study 20101291) and one positively adjudicated study in pivotal phase 3 study 20070337. The placebo controlled population patient had a confounding factor of a maladaptive fitting denture. The second patient in the pivotal phase 3 trial had a previous non serious event of periodontitis during the denosumab follow on period, during month 17. The clinical reviewer concluded that there is a concern for ONJ development with romosozumab.

Study 20110142 (still ongoing and not included in the drug application) had two cases that occurred at months 21 and 27. One case was in the Romosozumab-Alendronate arm at month 27 after 15 months of alendronate, and one case in the alendronate-alendronate arm, at month 21 on alendronate. The clinical reviewer concluded that alendronate treatment confounds the results as the anti-absorptive properties of the bisphosphonates are linked to both ONJ and AFF. The concern that romosozumab increases the risk of ONJ is supported by the fact that one of the patients positive ONJ patients had received romosozumab for one year prior to roll-over to alendronate.

5.1.5 Atypical Femoral Fractures

There were 5 cases of atypical femoral fractures (AFF) in patients receiving romosozumab. One case of AFF occurred in the 12 month placebo controlled portion of the pivotal phase 3 trials. Per the sponsor the patient had a history of prodromal pain in the fracture area and the sponsor classified it as an idiopathic event. The clinical reviewer did not agree because the patient had their fracture after 4 doses of romosozumab and had no prior exposure of bisphosphonate or denosumab therapy. The remaining four cases are in the ongoing blinded alendronate-controlled study with a time of onset of 502 to 1020 days after initiation of a double blind investigational product. The applicant unblended the information at DBRUP's request and found that three patients in the alendronate-alendronate arm of the study had AFF at months 16, 17, and 28. The remaining 2 cases were in the romosozumab-alendronate arm of the study had AFF at month 31 after 21 months on alendronate and one case of a femur fracture that was not adjudicated as AFF at month 28 after 16 months on alendronate. The clinical reviewer concluded that the clinical data supports concern for romosozumab as a risk for AFF in this patient population.

5.2 Adverse Events of Special Interest (AESI)

5.2.1 Hypocalcemia

The mechanism of action for romosozumab potentially correlates to decreases in serum calcium due to increased demand for calcium to increase bone formation. A sub study was done within the pivotal trial

at the time of enrollment to month 24 to characterize the subject indices of hypocalcemia (albumin corrected serum calcium level < 7.5 mg/dl) associated with 210 mg of romosozumab and calcium/vitamin D supplementation. There were no patients with hypocalcemic values within the group by the end of the study.

In the 12 month placebo controlled population, laboratory findings of calcium were taken and the National Cancer Institute Criteria for Common Terminology Adverse Events (CTCAE) were used to determine subject incidences > or = to Grade 3. Throughout the study, it was observed that there were no serious adverse events in the safety population and only one patient in the romosozumab group experienced an adverse event. While there was a 2.2% drop in serum calcium levels baseline in the romosozumab group within the first month of therapy, and none in the placebo group, both groups calcium levels normalized by month 12 for both groups within 1% of baseline and back to baseline at month 24.

Phase one study 20110227 had a single dose of romosozumab given to eight healthy subjects and eight subjects with stage four renal impairment or stage five chronic kidney disease (CKD). Patients with kidney disease are more prone to hypocalcemia due to abnormal renal loss of calcium. This study was done to see by comparison how healthy patients and kidney disease patients' calcium levels were affected. Calcium and Vitamin D supplementation were given to all patients. The largest decreases in serum calcium were among the stage five CKD patients and this group had hypocalcemia as the most frequently reported adverse event, and three patients in the stage four renal insufficiency group, while none of the healthy patients developed hypocalcemia. The clinical reviewer concluded that romosozumab can be used in renal failure patients but that calcium and vitamin D status should be monitored closely during therapy.

6 Expected Postmarket Use

Romosozumab is expected to be prescribed by primary care physicians, rheumatologists, and endocrinologists. As a subcutaneous injection, it is likely that patients will inject this product at home, after being taught proper injection technique. The risks will be communicated through labeling including a Medication Guide.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for romosozumab beyond routine pharmacovigilance, a Medication Guide, and labeling.

8 Discussion of Need for a REMS

Due to the imbalance of cardiovascular deaths, the clinical reviewer is recommending a complete response action for this application.

The risks of osteonecrosis of the jaw, atypical femoral fractures, hypersensitivity, and hypocalcemia can be communicated through labeling and a Medication Guide. These risks are observed with another

biologic treatment approved for the treatment of osteoporosis, Prolia. Prolia (denosumab) has risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, and hypersensitivity. These risks are included in the Prolia REMS (the REMS also includes the risk of skin infections), however none of these risks rise to the level of requiring a boxed warning. Prolia's RANKL inhibition reduces bone resorption, leading to frozen bone issues which can cause microfractures and greater incidences of osteonecrosis of the jaw and atypical femoral fractures.[12]

When comparing AFF, denosumab's pivotal trial had shown 79 subjects (48 in placebo, 31 in denosumab group) that sustained hip and femur fractures. The extension study confirmed further issues where 21 subjects had experienced fractures (14 in placebo/denosumab group and 7 in denosumab/denosumab group). In comparison, the placebo controlled population for Romosozumab had one subject adjudicated event of AFF, but three months prior to therapy they had a history of prodromal pain in the fracture area. The remaining four cases are in the ongoing blinded alendronate-controlled study with a time of onset of 502 to 1020 days after initiation of a double blind investigational product.

When comparing ONJ, denosumab's open label study had one case of ONJ that has been adjudicated and confirmed. While the phase 3 program convened an ONJ Adjudication Committee and found no cases identified, there have been documented cases of ONJ with denosumab use in the advanced cancer population. In the case of Romosozumab, One subject in the 12 month placebo controlled population (the romosozumab group and none in placebo) was identified, along with one patient in the phase three pivotal study (romosozumab/denosumab group). Both patients had confounding factors where the placebo controlled population patient had a maladaptive fitting denture, and the pivotal study patient had a previous non serious event of periodontitis. The study that is still ongoing and not included in the drug application is a blinded alendronate controlled study where two cases had occurred at months 21 and 27.

When comparing hypocalcemia, denosumab's pivotal trial had 3 subjects in placebo, 33 subjects with drug treatment after month 1 of therapy that had serum levels less than 8.5 mg/dl and were asymptomatic. Overall, 3.3% of subjects had serum calcium less than 8.5 mg/dl at day 10 for treatment naive patients in the extension study. There was a decrease in serum levels less than 8.5 mg/dL in 0.4% of women in placebo, 1.7% of women in denosumab group in the pivotal trials. A sub study was done within the romosozumab pivotal study to characterize the subject indices of hypocalcemia (albumin corrected serum calcium level < 7.5 mg/dl) associated with 210 mg of romosozumab and calcium/vitamin D supplementation. There were no hypocalcemic values in either treatment groups after the first month and returned to baseline by month 24.

Romosozumab's sclerostin inhibition leads to inhibiting bone resorption and promoting osteoblast formation. Given that the mechanism of action is different from denosumab, romosozumab had fewer incidences during the clinical development program of the risks of osteonecrosis of the jaw, atypical femoral fractures, hypersensitivity and hypocalcemia. Therefore, while romosozumab has similar risks to

[12] (Stephen Voss, 2010)

denosumab, the incidence rates of these risks in the clinical development program are significantly less in the romosozumab clinical development program.

With regard to cardiovascular events, new, unexpected safety findings from Study 20110142 and Study 20110174 (the phase 3 randomized, double-blind, active-comparator study of romosozumab followed by alendronate compared to alendronate alone) identified an imbalance of incidences of cardiovascular events, with higher incidences in the romosozumab group when compared to placebo. Final analyses of these studies are yet to be completed, as the studies ended in April, 2017.

Therefore at the time of this review, it has not been determined that the benefits of the drug outweigh the risks, and DRISK is unable to make an assessment of whether a REMS for romosozumab is necessary. The risk of cardiovascular events must be further characterized before DRISK is able to make a determination of whether a REMS is necessary to ensure the benefits outweigh the risks.

9 Conclusion and Recommendations

The review division recommends a complete response, therefore we are unable to formulate recommendations for risk management, specifically a REMS. Evaluation of the need for a REMS for romosozumab will be undertaken by DRISK after the Applicant addresses and responds to issues in the CR letter. Please send DRISK a new consult request at such time.

10. Materials Reviewed

The following is a list of materials informing this review:

1. Amgen, Clinical Review of Romosozumab, 2016.
2. Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis. American Association of Clinical Endocrinologists and American College of Endocrinology, 2016.
3. Cvetkovich, Therese. Prolia REMS 6 Year Assessment Report, November 7 2016.
4. M.S. Ominsky, et al, Effects of sclerostin antibodies in animal models of osteoporosis, Bone (2016).
5. Rothstein, Voss, et al. Summary Review for Denosumab [BLA (b) (4)] January 25, 2010.
6. Chang, T.D. Summary Review for Romosozumab [BLA 761062] May 3, 2017.
7. Chang, T.D. Clinical Review Update and Addendum [BLA 761062], June 13, 2017

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/s/

AMEET JOSHI
07/13/2017

JAMIE C WILKINS PARKER
07/13/2017