CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761392Orig1s000
761392Orig2s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF CARDIOLOGY, HEMATOLOGY, ENDOCRINOLOGY, AND NEPHROLOGY
DIVISION OF GENERAL ENDOCRINOLGY

NDA/BLA #s: 761392
Products: Ospomyv (denosumab-dssb), injectrion,
APPLICANT: Samsung Bioepis Co., Ltd.
FROM: Marina Zemskova, M.D., Deputy Director for Safety]
DATE: 2/12/2025

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;

(B) The seriousness of the disease or condition that is to be treated with the drug;

(C) The expected benefit of the drug with respect to such disease or condition;

(D) The expected or actual duration of treatment with the drug;

(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;

(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Ospomyv to ensure that the benefits of the drug outweigh the risks of severe hypocalcemia in patients with advance chronic kidney disease (CKD) including dialysis-dependent patients. In reaching this determination, we considered the following:

A. In the United States, the age-adjusted prevalence of osteoporosis at either the femur neck or lumbar spine or both among adults aged 50 and over is 12.6% and the prevalence of low bone mass, a precursor of osteoporosis, at either the femur neck or lumbar spine or both among adults aged 50 and over is 43.1%. This estimate is based on data from National Health and Nutrition Examination Survey (NHANES), 2017-2018[1]. CKD is a risk factor for osteoporosis. Among the NHANES III participants, osteoporosis was twice as common in those with eGFR < 60 mL/min than those with eGFR > 60 mL/min[2].

B. Osteoporosis is a bone disease defined by low bone mass and skeletal fragility that predisposes patients to risk of vertebral and nonvertebral fractures. Fracture, predominantly hip fracture, is associated with loss of mobility and increased. mortality. There are multiple factors that can contribute to fractures in patients with advanced CKD. In addition to age-related or other comorbid conditions-related bone loss and/or osteoporosis, CKD patients also have alterations in vitamin D and mineral metabolism. CKD-mineral bone disease (MBD) is a distinct syndrome encompassing mineral, bone, and calcific cardiovascular abnormalities that develop as a complication of CKD. Both age-related osteoporosis and CKD-MBD can lead to increased bone fragility and fracture. Fragility fractures due to osteoporosis and/or mineral and bone disorders associated with CKD-MBD comorbidity can decrease quality of life and increase overall mortality risk in this population.

C. Ospomyv is an interchangeable biosimilar product to Prolia (denosumab). Denosumab is a human monoclonal IgG2 antibody that targets the receptor activator of nuclear factor kappa B ligand (i.e., RANKL). Inhibition of RANK ligand binding to the RANK receptor underlies the efficacy of Prolia in treating all conditions for which it is indicated. Ospomyv has the same mechanism(s) of action, route of administration, dosage form, strengths, and conditions of use as those of Prolia. Since Ospomyv shares the same mechanism of action (i.e., functions as a RANKL inhibitor), efficacy across indications is extrapolated for Ospomyv. Denosumab has demonstrated effects on fracture risk and bone mineral density in multiple osteoporosis populations, including patients with CKD stages 1-3. Although the direct evidence of fracture risk reduction in advanced and dialysis-dependent CKD patients is limited (dialysis-dependent CKD patients were excluded and only small number of patients with advanced CKD were included in the denosumab clinical trials), denosumab's benefit in advanced CKD patients is expected based on the mechanism of action. Ability to identify patients who are likely to benefit from denosumab remains difficult given the challenges with determining the pathophysiology of altered bone metabolism in advanced and dialysis-dependent CKD patients.

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[1] Neda Sarafrazi, Ph.D., Edwina A. Wambogo, Ph.D., M.S., M.P.H., R.D., and John A. Shepherd, Ph.D. Osteoporosis or Low Bone Mass in Older Adults: United States, 2017–2018. NCHS Data Brief No. 405, March 2021.

[2] Nickolas T.L., McMahon D.J., Shane E. Relationship between moderate to severe kidney disease and hip
fracture in the United States. J. Am. Soc. Nephrol. 2006;17:3223–3232

D. The drug will be used chronically.

E. Ospomyv is highly similar to Prolia (see above) and is expected to have the same safety profile as Prolia. Denosumab-induced inhibition of bone resorption potentially impacts the contribution of exchangeable bone calcium to the overall calcium hemostasis, thereby affecting serum calcium levels and hypocalcemia is a well-recognized consequence of anti-resorptive therapy. In addition to hypocalcimia, denosumab has been associated with osteonecrosis of the jaw, atypical femur fracture, serious infections and dermatologic reactions. Prolia was approved with REMS (June 1, 2010) to mitigate the risks of hypocalcemia, osteonecrosis of the jaw, atypical femur fracture, serious infections and dermatologic reactions. Recently, a new safety signal of severe hypocalcimia in patients with advanced CKD including dialysis-dependent patients was identified (based on postmarketing safety data and the results of Centers for Medicare and Medicaid Services (CMS) studies conducted by FDA), therefore on November 7, 2023 SLC was issued for Prolia. In addition, DGE reviewed 8-year postmarketing safety data and concluded that the incidence rates of risk of other than hypocalcemia adverse events of special interest including osteonecrosis of the jaw, atypical femoral fractures, serious infections and dermatologic reactions were stable, had no impact on the benefit risk profile of Prolia and can be adequately mitigated through labeling. Based on the above findings, DGE and OSE determined that Prolia REMS must be modified to mitigate the risk of the new safety information of severe hypocalcimia in patients with advanced CKD and that the risks of hypocalcimia, osteonecrosis of the jaw, atypical fractures, serious infections and dermatologic reactions should be removed from the REMS.

F. Ospomyv is not a new molecular entity.
There are several FDA-approved treatment options in multiple drug classes for osteoporosis. However, there are limited data to support efficacy of these treatments in patients with advanced or dialysis dependent CKD. Treating bone disease in patients with advanced and dialysis dependent CKD is challenged by the difficulty in diagnosis and confirmation of altered bone metabolism responsible for the low bone mass and increased fracture risk; the variability of individual patient's underlying condition and risk factors; and the complex benefit-risk considerations of any of the approved osteoporosis treatments in this population. Use of any available therapy in this population requires careful individual consideration of benefit-risk, given the patient's specific medical history and risk factors. There is unmet medical need for safe and effective therapies that reduce fracture risk for dialysis-dependent and advanced CKD patients.

The elements of the REMS will be Communication Plan (CP) and a timetable for submission of assessments of the REMS.

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/s/

MARINA ZEMSKOVA
02/12/2025 09:08:04 AM

Division of Risk Management (DRM)
Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)
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(s)	761392
Goal Date (internal)	February 12, 2025
Nexus TTT #	2024-8269
Reviewer Name	Brian Caruth, Pharm.D., BCPS
	Yanick Elame, Pharm.D. (DMAMES)
Team Leader	Yasmeen Abou-Sayed, Pharm.D.
	Kathryn Marwitz, Pharm.D., MPH (DMAMES)
Associate Director	Page Crew, Pharm.D., MPH, BCPS (DMAMES)
Division Director (Acting)	Laura Zendel, Pharm.D.
Review Completion Date	February 11, 2025
Subject	Evaluation of proposed REMS
Trade Name	Ospomyv
Established Name	Denosumab-dssb
Applicant	Samsung Bioepis Co., Ltd.
Review Division	Division of General Endocrinology
Therapeutic Class	RANK ligand (RANKL) inhibitor
Formulation(s)	Single-dose prefilled syringe containing 60 mg in a 1 mL solution
Dosing Regimen	60 mg every 6 months as a subcutaneous injection in the upper arm, upper thigh, or abdomen

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Ospomyv (denosumab-dssb) Biologic Licensing Application (BLA) 761392 submitted by Samsung Bioepis Co., Ltd. on February 11, 2024 and last amended on January 23, 2025. Ospomyv is proposed as a biosimilar product to the reference listed drug (RLD) Prolia, BLA 125320. Ospomyv is under review in the Office of Therapeutic Biologics and Biosimilars (OTBB) and the Division of General Endocrinology (DGE). The Applicant is seeking approval for the following indications that are approved for the RLD:

- Treatment of postmenopausal women with osteoporosis at high risk for fractures
- Treatment to increase bone mass in men with osteoporosis at high risk for fractures
- Treatment of glucocorticoid-induced osteoporosis (GIOP) in men and women at high risk for fracture
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

The Prolia REMS, approved on June 1, 2010 and most recently modified on April 9, 2024 includes a communication plan (CP) and timetable for submission of assessments to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients associated with Prolia.

The elements of the Ospomyv REMS proposed by the Applicant are the same as those for the currently approved Prolia REMS and include the same communication plan and a timetable for submission of assessments. The requirements of the Ospomyv REMS will also apply to any unbranded denosumab-dssb products distributed by the Applicant.

DRM has determined that, as designed, the proposed REMS for Ospomyv is adequate, and will communicate the same key risk messages as the approved Prolia REMS to achieve the same level of safety. This review also includes the Division of Mitigation Assessment and Medication Error Surveillance's (DMAMES) evaluation of the proposed REMS Assessment Plan. DMAMES found the REMS Assessment Plan as submitted on January 13, 2025 to be acceptable.

The proposed Ospomyv REMS as submitted on January 23, 2025 is acceptable for approval.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Ospomyv (denosumab-dssb) biologic licenses application (BLA) 761392 to determine if the REMS achieves the same level of safety as the REMS for the reference listed drug (RLD), Prolia (denosumab), BLA 125320. The review also includes the Division of Mitigation Assessment and Medication Error Surveillance's (DMAMES) evaluation of the proposed REMS Assessment Plan. Ospomyv was submitted by Samsung Bioepis Co., Ltd. on February 11, 2024, last amended on January 23, 2025. This application is under review in the Office of Therapeutic Biologics and Biosimilars (OTBB) and Division of General Endocrinology (DGE). The Applicant is seeking approval for the same indications that are approved for the RLD:

- Treatment of postmenopausal women with osteoporosis at high risk for fractures
- Treatment to increase bone mass in men with osteoporosis at high risk for fractures
- Treatment of glucocorticoid-induced osteoporosis (GIOP) in men and women at high risk for fracture
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

The Applicant's proposed REMS consists of a communication plan (CP) and timetable for submission of assessments.

2 Background

2.1 Product Information

Denosumab is a human monoclonal IgG2 antibody that targets the receptor activator of nuclear factor kappa B ligand (i.e., RANKL). Ospomyv is proposed to be available as a single-dose prefilled syringe containing 60 mg in a 1 mL solution. The recommended dose is 60 mg every 6 months as a subcutaneous injection in the upper arm, upper thigh, or abdomen. Duration of treatment with Ospomyv is expected to be long term and likely administered in an outpatient setting.[a] The proposed indication, dosage, and presentation for Ospomyv are the same as Prolia. In addition to Prolia, one denosumab biosimilar, BLA 761362 (Jubbonti [denosumab-bbdz]), is also approved.

2.2 Prolia REMS

Prolia was approved with a REMS to ensure that the benefits outweighed the risk of osteonecrosis of the jaw, serious infection, and dermatologic reactions. The Prolia REMS was originally approved on June 1, 2010. The risks of hypocalcemia and atypical femur fracture were added to the REMS in 2012. The REMS has been modified fourteen times since approval and was last modified on April 9, 2024. Table 1 summarizes the currently approved REMS.

TABLE 1: SUMMARY OF APPROVED PROLIA REMS

REMS Goals	To mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Prolia
	To inform healthcare providers on the: • Risk of severe hypocalcemia with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m2) • Need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Prolia in patients with advanced chronic kidney disease
REMS Elements	Communication Plan • Patient Guide • REMS Letter for Healthcare Providers • REMS Letter for Professional Societies • REMS Website
Timetable for Submission of Assessments	18 months, 3, and 7 years from the date of the REMS modification (March 5, 2024)

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

2.3 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761392 relevant to this review:

- 01/19/24: FDA approved a Safety Labeling Change (SLC) for BLA 125320 pertaining to the risk of severe hypocalcemia in patients with advanced chronic kidney disease including dialysis-dependent patients[1]
- 02/11/24: BLA 761392 received for Ospomyv (denosumab-dssb) with an incomplete REMS
- 3/5/2024: Prolia REMS modification approved.[2] The REMS modification included revising the REMS to align the risk messaging in the REMS with the updated prescribing information (PI). The Prolia REMS goal was updated to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients. The REMS modification also removed the risks of ONJ, AFF, serious infections, and dermatologic reactions from the REMS, removed the MG as an element of the REMS, and revised the timetable for submission of assessments to 18-months, 3-years and 7- years from the date of modification.
- 03/14/24: FDA issued an Information Request (IR) to the Applicant to submit a REMS amendment with an updated proposed REMS aligning with the Prolia REMS modification approved on 03/05/24
- 04/11/24: The Applicant submitted a REMS amendment (sequence 0006) addressing FDA comments sent 03/14/24
- 11/20/24: FDA issued an IR to the Applicant to submit a REMS amendment to update the REMS materials with the trade name and include sections for Key Risk Messages (KRM) and Key Performance Indicators (KPI) in the REMS Supporting Document
- 12/06/24: The Applicant submitted a REMS amendment (sequence 0038) addressing FDA comments sent 11/20/24
- 12/17/2024: FDA issued an Advice Letter informing the Applicant of the conditionally acceptable determination for their proposed product nonproprietary name, denosumab-dssb
- 01/02/2025: FDA issued an IR to the Applicant to submit a REMS amendment to update the REMS materials with the nonproprietary name and reference the unbranded biological product in the REMS Document
- 01/13/25: The Applicant submitted a REMS amendment (sequence 0041) addressing FDA comments sent 01/02/25
- 01/21/2025: FDA issued an IR to the Applicant to submit a REMS amendment to update the REMS Document requirements for disseminating communication materials
- 01/23/25: The Applicant submitted a REMS amendment (sequence 0043) addressing FDA comments sent 01/21/25

3 Benefit Assessment

Biosimilarity of SB16 (denosumab-dssb) to US sourced Prolia (US-Prolia) was evaluated in a phase 1 pharmacokinetic (PK) similarity study (Study SB16-1001 [NCT04621318]) and a phase 3 comparative clinical study (Study SB16-3001 [NCT04664959]).

Study SB16-1001 was a 32-week, randomized, double-blind, three-arm, parallel group, single dose study in 168 health male subjects (56 subjects in each treatment arm) 28 to 55 years of age. Subjects were randomized to receive a 60 mg subcutaneous dose of either SB16 (denosumab-dssb), EU sourced Prolia (EU-Prolia) or US-Prolia. The primary outcome measures in study SB16-1001 were achieved for all three PK parameters and are summarized in Table 2.

TABLE 2: SUMMARY OF PRIMARY OUTCOME MEASURES IN STUDY SB16-1001

Outcome Measure (Measure Description)	Treatment Comparison and Similarity Criterion (90% Confidence Interval [CI] of the Geometric Least Squares [LS] Mean Ratios [0.80, 1.25])		
	SB16 and EU-Prolia	SB16 and US-Prolia	EU-Prolia and US-Prolia
AUC_{inf} Area under the concentration-time curve from time zero to infinity	(0.93, 1.10)	(0.91, 1.08)	(0.89, 1.07)
AUC_{last} Area under the concentration-time curve from time zero to the last quantifiable concentration	(0.94, 1.12)	(0.92, 1.10)	(0.89, 1.08)
C_{max} Maximum serum concentration	(0.95, 1.10)	(0.99, 1.15)	(0.97, 1.13)

Source: Section 5.3.3.1 CSR Study SB16-1001, Table 11-4, Table 11-5, and Table 11-6

Two subjects (one subject in the SB16 and one subject in the EU-Prolia group) with a major protocol deviation were not included in the analysis of Study SB16-1001. Pharmacodynamic (PD) data was not used to assess biosimilarity, however the clinical pharmacology reviewer evaluated the PD data to ensure that it did not conflict with the PK data.

Study SB16-3001 was a 24-month, randomized, double-blind, parallel group, multicenter, equivalence study in 457 female subjects with postmenopausal osteoporosis 55 to 80 years of age. Subjects were randomized to receive a 60 mg subcutaneous dose of either SB16 or EU-Prolia at month zero and six (main period). At month 12, subjects who had received EU-Prolia were randomized again to either continue EU-Prolia or were transitioned to SB16 (transition period). Subjects who had received SB16 continued to receive SB16 and followed the randomization procedure to maintain blinding. The demographics and disease characteristics were balanced between the treatment groups. The primary efficacy endpoint in study SB16-3001, the percent change from baseline in lumbar spine (LS) bone mineral density (BMD) at month 12 between the SB16 and EU-Prolia treatment groups was met. The difference in the mean percentage change from baseline in LS-BMD was 0.24 (90% CI [-0.34, 0.83]), when testing non-inferiority, and 0.41 (90% CI [-0.17, 1.00]), when testing non-superiority, and was within the prespecified margin (90% CI [-1.45, 1.45]).

The clinical review team concluded that biosimilarity was established between SB16 (denosumab-dssb), EU-Prolia, and US-Prolia. This determination relied on the pre-specified PK parameter results from study SB16-1001 and additional PK data from study SB16-3001.

4 Risk Assessment & Safe-Use Conditions

The primary safety review of SB16 relies on data from study SB16-3001 that evaluated SB16 in female subjects with postmenopausal osteoporosis. A total of 456 subjects were included in the study SB16-3001 dataset (225 subjects from the SB16 group and 231 subjects from the EU-Prolia group). One subject in the EU-Prolia group never received a dose of study drug and was not included in the dataset. Safety data from study SB16-1001 that evaluated SB16 in healthy male subjects was examined for known risks of denosumab.

There were no deaths reported in study SB16-3001. One death was reported in study SB16-1001 in a subject randomized to SB16. The death (completed suicide) was not attributed to SB16.

Serious treatment emergent adverse events (TEAEs) occurred in comparable proportions between the treatment groups (8/225 [3.6%] in SB16 and 8/231 [3.5%] in EU-Prolia) during the main period. Two subjects in the SB16 treatment group reported a serious adverse event (SAE) of fracture (ankle fracture and forearm fracture). In the transition period, two subjects who had received SB16 and continued to receive SB16 reported an SAE of fracture (femoral neck fracture and forearm fracture).

TEAEs that occurred in ≥ 3% of subjects and more frequently (risk difference ≥ 1%) in subjects randomized to SB16 in the main period or transition period are listed in Table 3.

TABLE 3: TREATMENT EMERGENT ADVERSE EVENTS IN STUDY SB16-3001

Main Period	Transition Period
Headache	Headache
Vitamin D Deficiency	Vitamin D Deficiency
Arthralgia	Hemorrhage
Arthritis	
Dyslipidemia	
Hypertension	
Urinary Tract Infection	
Diarrhea	

Source: Clinical reviewer generated report

The incidence of anti-drug antibodies (ADAs) was low and comparable between the treatment groups in both studies. No subjects who reported a TEAE related to hypersensitivity in either study were positive for ADAs. No neutralizing antibodies (NAbs) were detected in treatment groups in either study.

The clinical reviewer determined that none of the SAEs in study SB16-3001 appeared to be related to SB16. TEAEs were largely consistent with the known safety profile of denosumab. There was no meaningful difference between treatment groups in either study with respect to immunogenicity data (ADAs and NAbs) or safety differences, nor an unacceptable risk of transition in study SB16-3001.

4.1 HYPOCALCEMIA

Hypocalcemia, especially in patients with bone-mineral disorder, is a known risk for denosumab. The risk is highlighted in the US-Prolia prescribing information as a boxed warning. The Applicant assessed for hypocalcemia two weeks after the first study drug administration (when calcium nadir is anticipated). In study SB16-3001, the median change from baseline in serum calcium was comparable in both treatment groups at two weeks and all subsequent measurements following study drug administration during the main period and transition period.

5 Expected Postmarket Use

The prescriber and patient population for Ospomyv are expected to be similar to that of Prolia. Ospomyv is likely to be prescribed in an outpatient setting by primary care providers, endocrinologists, rheumatologists, and gynecologists familiar with osteoporosis therapy. Prescribers are expected to be familiar with the predicted risks of RANKL inhibitor therapy. Patients with advanced chronic kidney disease who are at greater risk for severe hypocalcemia are expected to receive coordinated care from prescribers who are familiar with chronic kidney disease-mineral bone disorder (CKD-MBD) to ensure appropriateness of therapy with Ospomyv.

6 Review of the Proposed REMS

On March 14, 2024, FDA advised the Applicant to update their proposed REMS to aligning with the Prolia REMS modification approved on March 5, 2024. The proposed REMS submitted on February 11, 2024, last amended on January 23, 2025 includes a communication plan (CP) and timetable for submission of assessments.

6.1 REMS GOALS

The proposed goals for the REMS for Ospomyv are the same as the RLD found in Table 1.

Reviewer Comment: *The proposed goals are acceptable.*

6.2 REMS REQUIREMENTS

The proposed elements for Ospomyv are the same as the currently approved REMS for the RLD and are found in Table 1. The proposed REMS materials are similar to the currently approved REMS for the RLD and include a:

- Patient Guide
- REMS Letter for Healthcare Providers
- REMS Letter for Professional Societies
- REMS Website

The REMS, as designed, will achieve the same level of safety as the REMS for the RLD as explained in detail below.

Reviewer Comment: *We find the REMS requirements acceptable.*

7 Timetable for Submission of Assessments

The Applicant must submit REMS assessments at 18 months, 3 years, and 7 years from the date of initial approval of the REMS.

Reviewer Comment: *The timetable for submission of assessments is the same as the RLD REMS. We find the timetable for submission of assessments acceptable.*

8 Supporting Document

The REMS Supporting Document contains the REMS program background information and a description of the operations of the REMS, including the details of the specifics of the distribution plan for the communication plan materials and included contingencies for undeliverable mail and email. The Applicant clarified how the REMS will operate, be assessed, and monitored to ensure compliance with the REMS program.

Reviewer Comment*: The information in the REMS Supporting Document, including the contingency plan for undeliverable mail and email, is similar to the RLD REMS. We find the REMS Supporting Document acceptable.*

8.1.1 Key Risk Messages (KRMs)

The KRMs identify the most critical safety information that stakeholders should know about the risk and safe use behaviors to mitigate the serious risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Ospomyv. The KRMs are based on the REMS goals and objectives and guide the messaging throughout the REMS materials. The proposed KRMs are as follows:

Healthcare Providers:

- There is a risk of severe hypocalcemia in patients with advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m^2), including dialysis-dependent patients
- There is a need to assess patients for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Ospomyv
- Coordinate care with health care providers with expertise in CKD-MBD for patients with advanced chronic kidney disease during treatment with Ospomyv

Patients:

- There is a risk of severe hypocalcemia (low calcium in the blood) in patients with advanced chronic kidney disease, including dialysis-dependent patients

Reviewer Comment*: The proposed KRMs are acceptable.*

8.1.2 Key Performance Indicator (KPI)

This section includes the KPI, KPI thresholds and supporting rationale, and what actions may be taken if the KPI thresholds are not met. The proposed KPIs for the Ospomyv REMS are as follows:

REMS Objective	KPI	Thresholds
Inform healthcare providers on the: 1. Risk of severe hypocalcemia in patients with advanced chronic kidney disease 2. Need to assess for presence of chronic kidney disease- mineral bone disorder (CKD- MBD) before initiating Ospomyv	% of healthcare provider knowledgeable on risk of severe hypocalcemia in patients with advanced CKD and need to assess for presence of CKD-MBD before initiating Ospomyv	≥ 80% targeted knowledge threshold

For assessments involving stakeholder knowledge surveys, the Draft Guidance for Industry: Survey Methodologies to Assess REMS Goals That Relate to Knowledge recommends that the generally accepted minimum targeted knowledge threshold for achieving understanding by stakeholders is the lower bound of the 95% confidence interval with targeted knowledge rate of 80% or higher for each REMS survey knowledge domain. KPIs at or above the target threshold indicate the REMS is functioning as designed. KPIs below the target threshold may potentially indicate that the REMS is not functioning as designed, is not meeting the objective, or requires regulatory actions. However, further investigation may be warranted to determine if other confounding factors are involved to explain the KPI results, and we will review the totality of the assessment data to inform the assessment of the goals and objectives. The targeted knowledge threshold may change with more experience with the REMS and accumulation of post-market data.

***Reviewer Comment**: The KPI is acceptable.*

8.1.3 REMS Assessment Plan

The REMS Supporting Document includes the Applicant's proposed REMS Assessment Plan. The proposed REMS Assessment Plan includes metrics on Outreach and Communication, Implementation and Operations, Health Outcomes and/or Surrogates of Health Outcomes, Knowledge, and an Overall Assessment of REMS Effectiveness. The Assessment Plan also includes metrics to inform on the KPI that may aid in determining if the REMS is operating as intended and meeting its goals and objectives.

***Reviewer Comment**: The Applicant appropriately addressed our comments and the Assessment Plan submitted on January 13, 2025 is acceptable. The Assessment Plan is included in the Appendix of this review and will be included in the action letter.*

9 Impact of a Separate REMS on Access, Burden, and Safety

9.1 Impact on Burden for Healthcare Providers

The currently approved Prolia REMS includes a communication plan without a requirement linked to prescribing or dispensing. Potential for perceived burden or confusion for healthcare providers may result due to dissemination of a REMS Letter for Healthcare Providers provided by each approved program. To reduce potential stakeholder burden for healthcare providers that may already be familiar with the risks associated with denosumab products, the Ospomyv REMS materials will communicate the same key risk messages as the Prolia REMS.

9.2 Impact on Access and Burden for Patients

Patient enrollment is not a requirement of the REMS and burden for patients is expected to be minimal. To reduce any potential burden for patients, the REMS materials and operational aspects of the proposed REMS are harmonized to the extent possible with the Prolia REMS to minimize confusion.

9.3 Impact on Safe Use of Denosumab

As designed, the proposed REMS for Ospomyv will provide the same level of safety as the approved Prolia REMS and is designed to minimize burden for stakeholders. We note that Ospomyv will potentially be the third approved denosumab product and with the approval of the REMS, dissemination of the Ospomyv REMS Letter for Healthcare Providers may inform a greater number of prescribers about the risks associated with denosumab products.

10 Discussion

The clinical review team recommends approval of Ospomyv based on the efficacy and safety information provided in the application. The serious risk associated with the RLD is severe hypocalcemia in patients with advanced chronic kidney disease, including dialysis-dependent patients. Prolia is subject to a REMS to mitigate this risk. A REMS is necessary to ensure the benefits of Ospomyv outweigh the risk of severe hypocalcemia in patients with advanced chronic kidney disease, including dialysis-dependent patients. The Applicant submitted the Ospomyv REMS proposal on February 11, 2024 and last amended on January 23, 2025. The proposed separate REMS consists of a communication plan (CP) and timetable for submission of assessments. The elements of the proposed REMS as the same as the currently approved REMS for the RLD.

We acknowledge that approving multiple different denosumab product REMS will introduce some burden on the healthcare system, however, the burden is expected to be manageable as the requirements for each REMS program are the same. The availability of an additional safe and effective biosimilar product for patients is expected to offset the burden of having multiple REMS programs. Through regular assessments of each REMS, we will monitor the safety and burden of these REMS programs and determine whether any modifications are needed in the future.

DRM determined that, as designed, the proposed REMS for Ospomyv will achieve the same level of patient safety as the approved Prolia REMS that was last modified on April 9, 2024.

11 Conclusion & Recommendations

DMAMES reviewed the Assessment Plan and concluded that the January 13, 2025 Assessment Plan submission was acceptable. DRM finds the proposed Ospomyv REMS to be acceptable and recommends approval of the REMS as submitted on January 23, 2025.

12 Appendices

12.1 Assessment Plan

Samsung Bioepis Co., Ltd. will conduct periodic assessments of the extent to which the REMS elements are meeting its goals. Assessments of the REMS will be provided to the FDA at 18 months, 3 years, and 7 years after initial approval of the REMS. Based on the information reported, the requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

The REMS Assessment Plan must include, but is not limited to, the following: For each metric provide the two previous, current, and cumulative reporting periods (if applicable), unless otherwise noted.

Outreach and Communication

1. REMS Communication Plan Activities (*provide data for the 18-month report only):
    a. *Number of Healthcare Providers (HCPs) (stratified by specialty) targeted by the REMS
    b. *Number of professional societies targeted, and which professional societies reported distribution of the REMS letter to their respective members
    c. *REMS Letters: A summary that includes the following information stratified by distribution waves (i.e., date distributed):
        i. Total number and percentage of hardcopy **REMS Letters for Healthcare Providers** mailed, returned, and resent after obtaining updated address
        ii. Total number and percentage of **REMS Letter for Professional Societies** emails successfully delivered, opened, and unopened. Include the total number and percentage of hard copy letters mailed after undeliverable email attempts or for which the email address was unavailable
    d. Number and specialty of prescribers who received the **Patient Guide**
    e. Date and name of the key professional meetings attended and corresponding information on the REMS materials displayed and/or distributed

Implementation and Operations

2. Program Implementation (*provide data for the 18-month report only):
    a. *Date of first commercial availability of Ospomyv
    b. *Date when the REMS Website went live
    c. Number of total visits and unique visits to the REMS Website
    d. Number and type of REMS materials downloaded or accessed
3. Utilization Data:
    a. Ospomyv utilization information including but not limited to indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)

Knowledge

4. Evaluation of Healthcare Provider's Knowledge:
    a. An evaluation of HCPs' understanding of the risks of severe hypocalcemia in patients with advanced chronic kidney disease via analysis of assessment survey results; and stratify results by HCP specialty (e.g., endocrinologist, rheumatologist, primary care provider)
    b. An evaluation of HCPs' understanding of the need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Ospomyv and stratify results by HCP specialty
    c. An evaluation of HCPs' understanding of the requirement to give each patient a copy of the **Patient Guide** via analysis of assessment surveys results

Health Outcomes and/or Surrogates of Health Outcomes

5. Safety Surveillance:
    a. A summary and analysis of all postmarketing case reports of severe hypocalcemia associated with Ospomyv, stratified by kidney function

Overall Assessment of REMS Effectiveness

The requirements for assessments of an approved REMS under section 505 1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

12.2 REMS MATERIALS

Training and Educational Materials

Patient:

1. Patient Guide

Communication Materials

2. REMS Letter for Healthcare Providers
3. REMS Letter for Professional Societies

Other Materials

4. REMS Website

13 References

[1] Prolia Supplemental Approval Letter. DARRTS Reference ID: 5312800. January 19, 2024.

[2] Prolia Supplemental Approval Letter. DARRTS Reference ID: 5339991. March 5, 2024.

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Division of Risk Management (DRM)
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	761392
BsUFA Goal Date	February 12, 2025
Nexus TTT#	2024-8269
Reviewer Name(s)	Brian Caruth, Pharm.D., BCPS
Team Leader	Yasmeen Abou-Sayed, Pharm.D.
Review Completion Date	November 20, 2024
Subject	Interim Review of proposed REMS
Established Name	Denosumab
Trade Name	Ospomyv – proposed interchangeable biosimilar to denosumab
Name of Applicant	Samsung Bioepis Co., Ltd.
Therapeutic Class	RANK ligand (RANKL) inhibitor
Formulation(s)	Single-dose prefilled syringe containing 60 mg in a 1 mL solution
Dosing Regimen	60 mg every 6 months as a subcutaneous injection in the upper arm, upper thigh, or abdomen

TABLE OF CONTENTS

1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed REMS for Ospomyv (SB16, denosumab), Biologics License application (BLA) 761392, submitted by Samsung Bioepis Co., Ltd. on February 12, 2024 and amended on April 11, 2024.

Ospomyv is a monoclonal antibody specific to receptor activator of nuclear factor kappa B ligand (RANKL) proposed as an interchangeable biosimilar to the United States approved Prolia, BLA 125320. The proposed indication, same as BLA 125320, for Ospomyv is for:

- Treatment of postmenopausal women with osteoporosis at high risk for fractures
- Treatment to increase bone mass in men with osteoporosis at high risk for fractures
- Treatment of glucocorticoid-induced osteoporosis (GIOP) in men and women at high risk for fracture
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

This application is under review in the Division of General Endocrinology (DGE). This interim review includes DRM's comments on the REMS proposal.

2. Regulatory History

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

- 02/12/24: BLA 761392 received for SB16 (denosumab) with an incomplete REMS
- 03/14/24: FDA issued an Information Request (IR) to the Applicant to submit a REMS amendment with an updated proposed REMS aligning with the Prolia REMS modification approved on 03/05/24
- 04/11/24: The Applicant submitted a REMS amendment (sequence 0006) addressing FDA comments sent 03/14/24

3. Comments to the Applicant

We have the following comments on your proposed REMS, submitted on April 11, 2024. Review of the REMS proposal is ongoing; these comments should not be considered final.

General Comments

- Submit the REMS Document and each REMS material as a separate file. The REMS Document and each REMS material should include a Clean Word, a Tracked Word, and a pdf formatted version.
- Revise references to the proposed product from (b) (4) to "Ospomyv"

REMS Document

- Revise the title [redacted] (b) (4) and include the proposed Proprietary name for the REMS. For example:

  Risk Evaluation and Mitigation Strategy (REMS) Document
  Ospomyv (denosumab-xxxx) REMS

- See redlined version of document (attached) for additional edits and formatting changes

REMS Supporting Document

- Include the following sections for Key Risk Messages (KRMs) and Key Performance Indicators (KPIs)

1. Key Risk Messages (KRMs)

   Key Risk Messages for Ospomyv for healthcare providers and patients:

   Key Risk Message for healthcare providers:

   - There is a risk of severe hypocalcemia in patients with advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m2), including dialysis-dependent patients.
   - There is a need to assess patients for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Ospomyv.
   - Coordinate care with health care providers with expertise in CKD-MBD for patients with advanced chronic kidney disease during treatment with Ospomyv.

   Key Risk Message for patients:

   - There is a risk of severe hypocalcemia (low calcium in the blood) in patients with advanced chronic kidney disease, including dialysis-dependent patients.

2. Key Performance Indicators (KPIs)

   The Ospomyv REMS will use the following KPI and associated targeted threshold for the objective of the Ospomyv REMS.

REMS Objective	KPI	Thresholds
Inform healthcare providers on the: 1. Risk of severe hypocalcemia in patients with advanced chronic kidney disease 2. Need to assess for presence of chronic kidney disease- mineral bone disorder (CKD- MBD) before initiating Ospomyv	% of healthcare provider knowledgeable on risk of severe hypocalcemia in patients with advanced CKD and need to assess for presence of CKD-MBD before initiating Ospomyv	≥ 80% targeted knowledge threshold

For more information on KRMs and KPIs see *Draft Guidance for Industry: Survey Methodologies to Assess REMS Goals That Relate to Knowledge, REMS Assessment: Planning and Reporting Guidance, and REMS Logic Model: A Framework to Link Program Design with Assessment.*

REMS Assessment Plan

- Begin the Assessment Plan with these 2 statements verbatim, "The REMS Assessment Plan must include, but is not limited to the following: For each metric provide the two previous, current, and cumulative reporting periods (if applicable), unless otherwise noted."
- For utilization metric 3a, edit to read, "Ospomyv utilization information including but not limited to indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)"
- Edit metric 4b and define CKD-MBD to read, "chronic kidney disease-mineral bone disorder (CKD-MBD)"
- Edit metric 5 to read, "Safety Surveillance"
- Edit metric 5a to read, "A summary and analysis of all post marketing case reports of severe hypocalcemia associated with Ospomyv, stratified by kidney function"

Submit the following revised REMS materials within 10 business days. Ensure that all Word versions include a setting that the author of comments and revisions can be identified (not anonymous). The next submission to the Gateway should include Clean Word, Tracked Word, and pdf formatted versions of the following documents:

	Materials	**Required Formats**
1	REMS Document	Tracked MS Word, Clean MS Word, PDF
2	REMS Letter for Healthcare Providers	Tracked MS Word, Clean MS Word, PDF
3	REMS Letter for Professional Societies	Tracked MS Word, Clean MS Word, PDF
4	Patient Guide	Tracked MS Word, Clean MS Word, PDF
5	REMS Website Screenshots	PDF
6	REMS Supporting Document	Tracked MS Word, Clean MS Word, PDF
7	Compiled REMS Document (consisting of REMS Document and appended REMS materials)	PDF

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