CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761444Orig1s000
761444Orig2s000

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: 761444
Products: Bildyos (denosumab-nxxp), injection
APPLICANT: Shanghai Henlius Biotech, Inc.
FROM: Marina Zemskova, M.D., Deputy Director for Safety
DATE: 8/21/2025

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 Bildyos 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. Bildyos 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. Bildyos has the same mechanism(s) of action, route of administration, dosage form, strengths, and conditions of use as those of Prolia. Since Bildyos shares the same mechanism of action (i.e., functions as a RANKL inhibitor), efficacy across indications is extrapolated for Bildyos. 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.

D. The drug will be used chronically.

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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

E. Bildyos 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. Bildyos 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
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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	761444
Goal Date (internal)	August 30, 2025
Nexus TTT #	2024-10713
Reviewer Names	Cristen Lambert, PharmD, DRM Yanick Elame, PharmD, Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)
Team Leaders	Kathryn Marwitz, PharmD, MPH, DMAMES Yasmeen Abou-Sayed, PharmD, DRM
Associate Directors	Page Crew, PharmD, MPH, BCPS (DMAMES) Suzanne Robottom, PharmD (DRM)
Review Completion Date	August 20, 2025
Subject	Evaluation of proposed REMS
Trade Name	Bildyos
Established Name	Denosumab-nxxp
Applicant	Shanghai Henlius Biotech, Inc.
Review Division	Division of General Endocrinology (DGE)
Therapeutic Class	RANK Ligand (RANKL) Inhibitor
Dosage Form(s)	Single-dose pre-filled syringe containing 60 mg in a 1 mL solution
Dosing Regimen	60 mg every 6 months as subcutaneous (SC) injection

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Bildyos (denosumab-nxxp) Biologics License Application (BLA) 761444, submitted by Shanghai Henlius Biotech, Inc., on August 30, 2024, and last amended on June 23, 2025. Bildyos is proposed as a biosimilar product to the reference listed drug (RLD) Prolia, BLA 125320. Bildyos is under review in the Office of Therapeutic Biologics and Biosimilars (OTBB) and the Division of General Endocrinology.

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 fracture
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture
- Treatment of glucocorticoid-induced osteoporosis in men and women with high risk for fracture
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

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

The elements of the Bildyos REMS proposed by Shanghai Henlius Biotech, Inc., are the same as those for the currently approved Prolia REMS and include a CP and a Timetable for Submission of Assessments.

DRM has determined that, as designed, the proposed REMS for Bildyos is comparable 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 June 23, 2025, to be acceptable.

The proposed Bildyos REMS as submitted on June 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 Bildyos (denosumab-nxxp) Biologics License Application (BLA) 761444, submitted by Shanghai Henlius Biotech, Inc., on August 30, 2024, and last amended on June 23, 2025, to determine if the REMS achieves the same level of safety as the REMS for the reference listed drug (RLD), Prolia (denosumab), BLA 125320. This application 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 same indications that are approved for the RLD Prolia:

1. Treatment of postmenopausal women with osteoporosis at high risk for fracture,

2. Treatment to increase bone mass in men with osteoporosis at high risk for fracture,
3. Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture,
4. Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, and
5. 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 a 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). Current US approved denosumab products include Prolia (60 mg/1 mL in a pre-filled syringe or PFS) and Xgeva (120 mg/1.7 mL or 70 mg/mL in a single-dose vial) approved under BLA 125320 from Amgen Inc in 2010, and denosumab biosimilars included in the table below.

Table 1: Approved denosumab biosimilars

Proper Name	Trade Name	Date Approved	Application Number
denosumab-bbdz	Jubbonti (60 mg/1 mL PFS) Wyost (120mg/1.7 mL or 70 mg/mL single-dose vial)	March 5, 2024[1]	BLA 761362
denosumab-dssb	Ospomyv (60 mg/1 mL PFS) + unbranded generic Xbryk (120mg/1.7 mL or 70 mg/mL single-dose vial) + unbranded generic	February 13, 2025[2]	BLA 761392
denosumab-bmwo	Stoboclo (60 mg/1 mL PFS) Osenvelt (120mg/1.7 mL or 70 mg/mL single-dose vial)	February 28, 2025[3]	BLA 761404
denosumab-bnht	Conexxence (60 mg/1 mL PFS) + unbranded generic Bomyntra (120 mg/1.7 mL or 70 mg/mL single-dose vial and PFS) + unbranded generic	March 25, 2025[4]	BLA 761398

Shanghai Henlius Biotech, Inc. (Shanghai) developed HLX14 (denosumab-nxxp) under proprietary names Bildyos and Bilprevda as interchangeable biosimilars to US-Prolia and US-Xgeva, respectively. Shanghai proposed the same indications, dosages, and presentations for HLX14 under Bildyos and Bilprevda to US-Prolia and US-Xgeva, respectively.

The recommended dose for Bildyos is a 60 mg subcutaneous (SC) injection every 6 months[a] to be administered by healthcare providers to patients in a clinical setting. Denosumab products are also

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

approved for similar indications in the European Union. In the US, Prolia is approved with a REMS to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease, including dialysis-dependent patients (see Section 2.2).

2.2 PROLIA REMS

Prolia was approved in 2010 with a REMS to ensure that the benefits outweighed the risk of osteonecrosis of the jaw, serious infection, and dermatologic reactions. The risks of hypocalcemia and atypical femur fracture were added to the REMS in 2012. Notably, a major modification was approved in March 2024 to remove four of the five risks and refocus the REMS solely on hypocalcemia. This was in response to a Safety Labeling Change (SLC) issued in November 2023 concerning hypocalcemia in patients with advanced kidney disease, including dialysis-dependent patients. This modification consisted of the following:

- Revised the REMS goal and risk messaging concerning hypocalcemia to specifically focus on patients with advanced kidney disease, including dialysis-dependent patients.
- Revised the REMS goal and risk messaging to remove the risks of ONJ, AFF, serious infections, and dermatological reactions.
- Removed the medication guide (MG) as an element of the REMS.

See table below describing the current goal and elements of the Prolia REMS.

Table 2: Summary of Approved Prolia REMS

REMS Goal	To mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-depending patients, associated with Prolia.
	Inform healthcare providers on: • Risk of severe hypocalcemia in patients with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) • 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: REMS Letter for Healthcare Providers, REMS Letter for Professional Societies, Patient Guide, and REMS Website to communicate safety information to healthcare providers.
Timetable for Submission of Assessments	18-months, 3-years, and 7-years from date of REMS modification approval, March 5, 2024.

2.3 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761444 relevant to this review:

- 8/30/24: BLA 761444, HLX14 (denosumab) submitted under the 351 (k) regulatory pathway as a biosimilar and interchangeable denosumab biological product to US-licensed Prolia and US-licensed Xgeva with the same respective indications, dosages, and presentations.
- 11/6/24: Applicant informed via Filing Communication Letter[5] that their proposed REMS must be submitted in Word and .pdf format to comprise a complete REMS submission.
- 12/4/24: Applicant submitted a REMS amendment[6] as a response to the information request communicated in the Filing Communication Letter.
- 5/7/25: Agency sent comments to the Applicant requesting revisions to the REMS Document, inclusion of Key Risk Messages (KRMs) and Key Performance Indicators (KPI) in the REMS Supporting Document, and revisions to the REMS Assessment Plan.
- 5/15/25: Applicant submitted a REMS amendment in response to the comments sent on May 7, 2025.
- 6/16/2025: Agency sent comments to the Applicant requesting editorial revisions to the REMS Document, updating the nonproprietary name denosumab to include the conditionally acceptable suffix in all REMS materials, and revisions in the REMS Supporting Document.
- 6/23/2025: Applicant submitted a REMS amendment in response to the comments sent on June 16, 2025.

3 Benefit Assessment

The Applicant submitted a PK Similarity Study (Study HLX14-001) and a comparative clinical study (Study 002-PMOP301) in support of the biosimilarity of HLX14 to US-Prolia. The Applicant used non-U.S.-licensed comparator product (EU-Prolia[b] and CN-Prolia[c]) to support their assessment of biosimilarity.

Study HLX14-001 was a two-part, randomized, double-blind, parallel group active-controlled, three-way pairwise study in healthy subjects to compare the pharmacokinetics (PK), safety, and immunogenicity of HLX14 (60 mg/mL), US-Prolia, EU-Prolia, and CN-Prolia. Part 1 (n=24) was a pilot PK study conducted in healthy adult male subjects randomized 1:1 comparing HLX14 and EU-Prolia as a single dose (60 mg SC). Part 2 (n=228) consisted of subjects randomized 1:1:1:1 comparing HLX14 vs US-Prolia vs EU-Prolia vs CN-Prolia as a single dose (60 mg SC). PK similarity between HLX14, US-Prolia, and EU-Prolia was demonstrated since the 90% confidence intervals (CI) for the geometric mean ratios for the tested PK

[b] European Union (EU) approved Prolia (EU-Prolia)

[c] China sourced Prolia (CN-Prolia)

parameters (AUC_{last}[d], $AUC_{0\text{-}inf}$[e] and C_{max}[f]) were all within the prespecified PK similarity criteria (i.e. 80%-125%).[7]

Study HLX14-002-PMOP301 was a phase III randomized, double-blind, international, multicenter, parallel-controlled study to compare the efficacy, pharmacodynamics (PD), safety, PK, and immunogenicity of HLX14 vs. EU-Prolia. In Study HLX14-02-PMOP301, postmenopausal women with osteoporosis at high risk of fracture received three subcutaneous (SC) injections of 60 mg HLX14 or EU-Prolia once every 6 months. In the Main Period (baseline to week 52) 256 subjects received HLX14 and 258 subjects received EU-Prolia. In the Extension Period (week 52-78), 220 subjects assigned to EU-Prolia in the Main Period were re-randomized to receive a third dose of either EU-Prolia (110 subjects) or HLX14 (110 subjects). After administration of HLX14 or EU-Prolia, the serum denosumab concentration profiles were comparable, and a single transition treatment from EU-Prolia to HLX14 did not impact the PK evaluation results.[7]

The Office of Clinical Pharmacology (OCP) determined Study HLX14-001 and HLX14-002-PMOP301 support a demonstration that HLX14 has no clinically meaningful differences from US-Prolia and US-Xgeva. OCP concluded from Study HLX14-001 that the PK portion of the scientific bridge was established and the Office of Pharmaceutical Products (OPQ) determined the analytical component of the scientific bridge was established, which support using the clinical and analytical data generated from EU-Prolia (Study 002-PMOP301) to demonstrate biosimilarity between HLX14 and US-Prolia, and between HLX14 and US-Xgeva. The Review Team recommends approval for HLX14 as a biosimilar to US-Prolia and US-Xgeva.[7] The Review Team recommends a Provisional Determination that HLX14 meets the applicable standards for interchangeability with US-Prolia and US-Xgeva, but the Agency is unable to approve any HLX14 injection for SC product as interchangeable with US-Prolia or US-Xgeva because of unexpired first interchangeable exclusivity for BLA 761362 (Jubbonti and Wyost).[7]

4 Risk Assessment & Safe-Use Conditions

The primary safety review of HLX14 relies on data from the comparative clinical study (HLX14-002-PMOP301) and the PK similarity study (HLX14-001). The safety population was defined as consisting of all subjects who received at least one Investigation Product administration during the study period and safety data were not combined due to study population and design differences.

There were no reported deaths in either study.

In study HLX14-002-PMOP301, the number of patients experiencing one or more adverse events was comparable across all treatments within the Main Period and the Extension Period. Thirty-nine subjects

[d] AUC_{last} = Area under serum concentration versus time curve from time zero to the last observation/infinity

[e] $AUC_{0\text{-}inf}$= Area under serum concentration versus time curve from time zero to infinity

[f] C_{max} = maximum observed serum study drug concentration

experienced a serious adverse event (SAE) in the Main Period, with 23 (9%) in the HLX14 group and 16 (6.2%) in the EU-Prolia group. In the Extension Period, 1 SAE was reported in each treatment arm (EU-Prolia/HLX14, EU-Prolia/EU-Prolia, HLX14/HLX14). None of the SAEs were determined to be related to study drug. In study HLX14-001 Part 2, the adverse events by grading were comparable between arms. Three patients discontinued from study HLX14-002-PMOP301 due to an adverse event, and all were during the Main Period on the EU-Prolia arm, none of which appeared to be related to study drug.

In study HLX14-001, one subject in the US-Prolia arm experienced a SAE of synovitis. The adverse events by grading were comparable between arms and there were no reported discontinuations from the study due to an adverse event.

The clinical reviewer did not identify any clinically meaningful differences in safety between HLX14 and US-Prolia or EU-Prolia.

4.1 HYPOCALCEMIA

Hypocalcemia, especially in patients with BMD, is a known risk for denosumab. The risk is highlighted in the US-Prolia prescribing information as a Boxed Warning. The risk of hypocalcemia is greater in patients with severe renal impairment, and study HLX14-002-PMOP301 excluded patients with an estimated glomerular filtration rate < 30 milliliters (mL) per minute. In the Main Period of study HLX14-002-PMOP301, subjects were required to have a normal corrected calcium at baseline and to receive daily calcium and vitamin D from screening until the end of study. The expected calcium nadir is expected two weeks post injection of denosumab, and calcium labs were first collected in the study at week 4. Calcium shift analyses were performed using uncorrected calcium and compared to baseline at Week 4 and Week 26. The median change in calcium was low and comparable in both arms. The incidence of subjects with hypocalcemia during treatment was similar between both arms and most shifts occurred during the first two weeks of treatment. During the Extension Period, subjects received the final dose of study drug at Month 12, so calcium levels were checked at Month 15 and Month 18. The median change in calcium was low and comparable in all arms.

In study HLX14-001, adverse events of special interest (AESI) were rare with hypocalcemia being the most common AESI. The number of patients in the HLX14 arm of Part 2 that experienced hypocalcemia [n=1 (1.7%)] was comparable to the US-Prolia, EU-Prolia, and CN-Prolia arms [n=1 (1.8%), n=2 (3.6%), n=1 (1.8%)], respectively.[7]

5 Expected Postmarket Use

The prescriber and patient population for Bildyos are expected to be similar to that of Prolia. Bildyos 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 CKD-MBD to ensure appropriateness of therapy with Bildyos.

6 Review of the Proposed REMS

The proposed Bildyos REMS was submitted on August 30, 2024, and amended on December 4, 2024, May 15, 2025, and June 23, 2025. The Bildyos REMS includes a CP and timetable for submission of assessments.

6.1 REMS GOALS

The proposed goal of the Bildyos REMS is to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Bildyos.

The proposed objective is to inform healthcare providers on:

- Risk of severe hypocalcemia in patients with advanced chronic kidney disease (estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2)
- Need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Bildyos in patients with advanced chronic kidney disease

Reviewer's Comments: *The proposed goal and objective are acceptable. The REMS goal and objective for Bildyos are the same as the currently approved goal for the Prolia REMS.*

6.2 REMS REQUIREMENTS

The proposed elements for Bildyos are the same as the currently approved REMS for the RLD (see Table 2). The proposed REMS materials are the same as the currently approved REMS for the RLD and include the *REMS Letter for Healthcare Providers*, *REMS Letter for Professional Societies*, *Patient Guide*, and *REMS website*. There are some minor operational differences in the proposed REMS. The REMS, as designed, will achieve the same level of safety as the REMS for the RLD as explained in detail below.

Reviewer Comments: *We agree with the Applicant's proposed Bildyos REMS because the requirements are similar to the RLD REMS, and it is expected to achieve the same level of safety.*

7 Timetable for Submission of Assessments

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

Reviewer Comments*: 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 Bildyos REMS Supporting Document contains the REMS background information and a description of the operations of the REMS, including the details of the specifics of the plan for communication of educational materials and dissemination. The Applicant must ensure that healthcare providers who are

likely to prescribe Bildyos are mailed the *REMS Letter for Healthcare Providers* and attached Prescribing Information within 60 days of the date Bildyos is first commercially available. The Applicant must also email the *REMS Letter for Professional Societies* and attached Prescribing Information within the same time frame. The Applicant must make the materials available on the REMS website, disseminate it through field-based sales and medical representatives, and disseminate and prominently display at Professional Meetings. The proposal includes a plan for returned mail and undeliverable emails. The REMS website includes a description of the Bildyos REMS, links to REMS materials, Prescribing Information, and Medication Guide, and information on reporting adverse events associated with Bildyos. The Applicant clarified how the REMS will operate, be assessed, and monitored to ensure compliance with the REMS program.

Reviewer Comments: *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 Supporting Document acceptable.*

8.1.1 Key Risk Messages (KRMs)

The KRMs identify the most critical safety information that participants should know about the risk and safe use behaviors to mitigate the serious risk of severe hypocalcemia in patients with advanced chronic kidney disease, including dialysis-dependent patients. 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 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 Bildyos.
- Coordinate care with health care providers with expertise in CKD-MBD for patients with advanced chronic kidney disease during treatment with Bildyos.

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(s) (KPIs)

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

- % of healthcare providers knowledgeable on risk of severe hypocalcemia in patients with advanced CKD and need to assess for presence of CKD-MBD before initiating Bildyos.

The targeted knowledge threshold is greater than or equal to 80%. For assessments involving participant knowledge surveys, *the Draft Guidance for Industry: Survey Methodologies to Assess REMS Goals That Relate to Knowledge* (February 2019) recommends that the generally accepted minimum targeted knowledge threshold for achieving understanding by participants 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 may indicate the REMS is functioning as designed and is meeting the objective. 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. The targeted 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, Knowledge, Health Outcomes and/or Surrogates of Health Outcomes, and an Overall Assessment of REMS Effectiveness. The Assessment Plan also includes metrics to inform the KPI, which may aid in determining if the REMS is operating as intended and meeting its goals and objectives.

Reviewer's Comments*: DMAMES reviewed the initial December 4, 2024 submission of the Assessment Plan located in the REMS Supporting Document and requested the Applicant make revisions. Comments with requested revisions were communicated to the Applicant in the May 7, 2025 Agency comments. The Applicant accepted all of requested revisions in their May 15, 2025 REMS amendment. Additionally, the Applicant did not propose any new changes to the REMS Assessment Plan with their June 23, 2025 REMS Amendment.*

Of note, DMAMES did not review the Applicant's Appendix I "Effectiveness in Conveying Safety Information to Healthcare providers Prescribing Bildyos" included in the REMS Supporting Document. DMAMES defers review of proposed survey methodologies until after action is taken. A recommendation to submit proposed REMS assessment methodologies for Agency review will be included in the action letter.

The Assessment Plan submitted on June 23, 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 CP without requirements 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 REMS. To reduce potential participant burden for healthcare providers that may already be familiar with the risks associated with denosumab products, the Bildyos 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 Bildyos will provide the same level of safety as the approved Prolia REMS and is designed to minimize burden for participants. We note that Bildyos will potentially be the fifth approved denosumab product and with the approval of the REMS, dissemination of the *Bildyos REMS Letter for Healthcare Providers* may inform a greater number of prescribers about the risks associated with denosumab products.

10 Discussion

The Division of General Endocrinology recommends approval of Bildyos 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 CKD, including dialysis-depending patients. Prolia is subject to a REMS to mitigate this risk. A REMS is necessary to ensure the benefits of Bildyos outweigh the risk of severe hypocalcemia in patients with advanced CKD, including dialysis-depending patients. The Applicant submitted the Bildyos REMS proposals on August 30, 2024, December 4, 2024, May 15, 2025, and last amended June 23, 2025. The proposed separate REMS consists of a CP and a 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 REMS will introduce some burden on the healthcare system. However, the burden is expected to be manageable as the requirements and risk messaging for each REMS are the same across all denosumab REMS programs and the programs do not require providers or patients to enroll. The availability of an additional safe and effective biosimilar product for patients is expected to offset the burden of having multiple REMS. Through regular

assessments of each REMS, we will monitor the REMS risk and burden of these REMS and determine whether any modifications are needed in the future.

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

11 Conclusion & Recommendations

DRM finds the proposed Bildyos REMS to be acceptable and recommends approval of the REMS as submitted on June 23, 2025.

12 Appendix

12.1 Bildyos REMS Assessment plan

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 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 Letter for Healthcare Providers** mailed, returned, and resent after obtaining correct 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 scientific meetings attended and corresponding information on the REMS materials displayed and/or distributed.

Implementation and Operations

2. Program Implementation (*Provide data for 18-month report only):
    a. *Date of first commercial availability of Bildyos
    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. Bildyos utilization information including but not limited to indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)

Knowledge

4. Evaluation of HCPs' knowledge:
    a. An evaluation of HCPs' understanding of the risk 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 Bildyos 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 survey results.

Health Outcomes and/or Surrogates of Health Outcomes

5. Safety Surveillance:
    a. A summary and analysis of all post-marketing case reports of severe hypocalcemia associated with Bildyos, stratified by kidney function.

Overall Assessment of REMS Effectiveness

6. 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.

12.2 BILDYOS REMS MATERIALS

Training and Education 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] Cabellon, N. DGE. Approval of denosumab biosimilar, BLA 761362, March 5, 2024.

[2] Johnson, J. Approval of denosumab biosimilar, BLA 761392, February 13, 2025.

[3] Cabellon, N. DGE. Approval of denosumab biosimilar, BLA 761404. February 28, 2025.

[4] Van der Waag, J. OCHEN. Approval of denosumab biosimilar, BLA 761398, March 25, 2025.

[5] Lee, A. DGE. Filing Communication for HLX14 (denosumab) BLA 761444, November 6, 2024.

[6] Shanghai Henlius Biotech, Inc. REMS Correspondence/Response to FDA's information request letter dated November 6, 2024; December 4, 2024.

[7] DGE, OTBB. DRAFT BMER for BLA 761444 HLX14 (denosumab), July 10, 2025.

7 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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	761444
BsUFA Goal Date	August 30, 2025
Nexus TTT#	2024-10713
Reviewer Name	Cristen Lambert, PharmD
DRM Team Leader	Yasmeen Abou-Sayed, PharmD
Review Completion Date	June 12, 2025
Subject	Interim Review of proposed REMS
Established Name	denosumab-nxxp
Trade Name	Bildyos – proposed interchangeable biosimilar to denosumab
Name of Applicant	Shanghai Henlius Biotech, Inc.
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

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed REMS for Bildyos (HLX14, denosumab), Biologics License application (BLA) 761444, submitted by Shanghai Henlius Biotech, Inc. on August 30, 2024, and amended on December 4, 2024, and May 15, 2025.

Bildyos is a monoclonal antibody specific to receptor activator of nuclear factor kappa B ligand (RANKL) proposed as an interchangeable biosimilar to United States (US) approved Prolia. The proposed indication for Bildyos is as follows:

- 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.

This application is under review in the Division of General Endocrinology (DGE).

This interim review discusses the following: DRM's comments on the REMS proposal

2. Regulatory History

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

- 8/30/24: BLA 761444, HLX14 (denosumab) submitted under the 351 (k) regulatory pathway as a biosimilar and interchangeable denosumab biological product to US-licensed Prolia and US-licensed Xgeva with the same respective indications, dosages, and presentations.
- 11/6/24: Applicant informed via Filing Communication Letter[1] that their proposed REMS must be submitted in Word and .pdf format to comprise a complete REMS submission.
- 12/4/24: Applicant submitted a REMS amendment[2] as a response to Information Request.
- 5/7/25: Agency sent comments to the Applicant requesting revisions to the REMS Document, the REMS Supporting Document to include Key Risk Messages (KRMs), and the REMS Assessment Plan.[3]
- 5/15/25: Applicant submitted an updated REMS as a response to the comments sent on May 7, 2025.

3. Comments to the Applicant

We have the following comments on your proposed REMS, submitted on August 30, 2024, and amended on December 4, 2024, and May 15, 2025. Review of the REMS proposal is ongoing; these comments should not be considered final.

General Comment

- Revise references to nonproprietary name denosumab to include the conditionally acceptable suffix for Bildyos. For example: (denosumab-nxxp)

REMS Document

- Remove reference to (b) (4) from the REMS Document since the Applicant is responsible for all REMS requirements. Refer to the appended redlined REMS Document for details regarding these edits.

REMS Supporting Document

- Consider including the description of interpreting a key performance indicator (KPI) in the KPI section:

  KPIs at or above the target threshold may indicate the REMS is functioning as designed and is meeting the objective. KPIs below the target threshold may not necessarily 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. The targeted threshold may change with more experience with the REMS and accumulation of post-market data.

Submit the following revised REMS materials within 10 business days**.** Ensure that all Word versions include a setting which 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, if they have been revised:

	Materials	**Required Formats**
1	REMS Document	Tracked MS Word, Clean MS Word, PDF
2	Patient Guide	Tracked MS Word, Clean MS Word, PDF
3	REMS Letter for Healthcare Providers	Tracked MS Word, Clean MS Word, PDF
4	REMS Letter for Professional Societies	Tracked MS Word, Clean MS Word, PDF
5	REMS Website	Tracked MS Word, Clean MS Word, 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

[1] Lee, A. DGE. Filing Communication for HLX14 (denosumab) BLA 761444, November 6, 2024.

[2] Shanghai Henlius Biotech, Inc. REMS Correspondence/Response to FDA's information request letter dated November 6, 2024; December 4, 2024.

[3] Lee, A. DGE. Information Request for HLX14 (denosumab) BLA 761444, May 7, 2025.

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
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Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761444
BsUFA Goal Date	August 30, 2025
Nexus TTT#	2024-10713
Reviewer Name	Cristen Lambert, PharmD
DMAMES Team Leader	Kathryn Marwitz, PharmD, MPH
DMAMES Associate Director	Page Crew, PharmD, MPH, BCPS
DRM Team Leader	Yasmeen Abou-Sayed, PharmD
Review Completion Date	May 6, 2025
Subject	Interim Review of proposed REMS
Established Name	denosumab-xxxx
Trade Name	Bildyos – proposed interchangeable biosimilar to denosumab
Name of Applicant	Shanghai Henlius Biotech, Inc.
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Formulation(s)	Single-dose prefilled syringe containing 60 mg in a 1 mL solution
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- 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.

This application is under review in the Division of General Endocrinology (DGE).

This interim review discusses the following: DRM's comments on the REMS proposal as well as the Division for Mitigation Assessment and Medication Error Surveillance (DMAMES)'s review of the REMS Assessment Plan.

2. Regulatory History

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

- 8/30/24: BLA 761444, HLX14 (denosumab) submitted under the 351 (k) regulatory pathway as a biosimilar and interchangeable denosumab biological product to US-licensed Prolia and US-licensed Xgeva with the same respective indications, dosages, and presentations.
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- 12/4/24: Applicant submitted a REMS amendment[2] as a response to Information Request.

3. Comments to the Applicant

We have the following comments on your proposed REMS, submitted on August 30, 2024 and amended on December 4, 2024. Review of the REMS proposal is ongoing; these comments should not be considered final.

REMS Document

- Use the full Applicant name (Shanghai Henlius Biotech, Inc.) throughout the REMS Document
- Remove the placeholder, "(Approval date is pending)" in section *IV. REMS Assessment Timetable* since the approval date will be inserted in *Section I. Administrative Information* at the time of approval.

REMS Supporting Document

- Include a section for Key Risk Messages (KRMs)

KRMs identify the most critical information for stakeholders to know about the risk and safe use behaviors to mitigate the risk. The KRMs should be based on the proposed REMS goals and objectives and should guide the messaging throughout the REMS materials. For more information on KRMS see *Draft Guidance for Industry: Survey Methodologies to Assess REMS Goals That Relate to Knowledge*, *REMS Assessment: Planning and Reporting Guidance*

We are providing the following suggested KRMs for the Bildyos REMS. Include a section on KRMs in the REMS Supporting Document before the Assessment Plan.

Key Risk Messages for Bildyos 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 Bildyos.
- Coordinate care with health care providers with expertise in CKD-MBD for patients with advanced chronic kidney disease during treatment with Bildyos.

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.

- REMS Assessment Plan
  - Add the following two introductory statements at the beginning of the REMS Assessment Plan:

    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.

  - In metric 1.c.ii, revise [redacted] (b) (4) to "REMS Letter for Professional Societies"
  - Add the word "such" to the last metric, as shown underlined here: 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 <u>such</u> elements should be modified.

[redacted] (b) (4)

(b) (4)

Key Performance Indicators (KPIs)

KPIs are measures essential in determining whether the REMS is functioning as designed and the targeted thresholds help determine whether the REMS is meeting the objectives or whether further evaluation or changes are warranted to improve compliance with the REMS.

The following KPIs should be included in the REMS Supporting Document before the REMS Assessment Plan in the REMS Supporting Document.

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 Bildyos	% 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 Bildyos	≥ 80% targeted knowledge threshold

KPIs at or above the target threshold may indicate the REMS is functioning as designed and is meeting the objective. KPIs below the target threshold may not necessarily 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. The targeted threshold may change with more experience with the REMS and accumulation of post-market data.

Submit the following revised REMS materials within 10 business days**.** Ensure that all Word versions include a setting which 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:

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