CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761404Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

REMS Assessment Plan Review MEMO

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)

*****This document may contain information that cannot be released to the public*****

Application Type	BLA
Application Number	761404
Task Tracking Tool Number	2024-9234*
Submission Type/Number	Original-1/36
Submission Date	February 17, 2025
Reviewer	Yanick Elame, PharmD
Team Lead	Kathryn Marwitz, PharmD, MPH
Associate Director	Page Crew, PharmD, MPH, BCPS
Review Completion Date	February 19 2025
Non-Proprietary Name	Denosumab-bmwo
Proprietary Name	Stoboclo
Subject	Review of Stoboclo Risk Evaluation and Mitigation Strategies (REMS) Assessment Plan Memo
Applicant	Celltrion Inc.

*Refer to the May 28, 2024 review in DARRTS for the initial review associated with this Task Tracking Tool Number

Introduction

This memo is in reference to the Risk Evaluation and Mitigation Strategy (REMS) Assessment Plan for the proposed Stoboclo REMS (hereafter, Stoboclo REMS). Refer to the May 28, 2024[a] Agency review and the February 13, 2025[b] Agency Information Request for additional background information.

Background and Discussion

On November 30, 2023, the Applicant submitted a 351(k) Biologics License Application (BLA) for a proposed (b) (4) biosimilar product to Prolia. The BLA included a proposed REMS that was comparable to the approved REMS for Prolia at the time (November 2023).[c]

On April 24, 2024[d], the Applicant resubmitted for review a REMS amendment that included a revised goal which was aligned with the goal for the Prolia REMS. The submission included a proposed REMS Assessment Plan, included within the REMS Supporting Document.

The Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) reviewed the proposed Assessment Plan and comments were sent to the Applicant on May 30, 2024.[e]

On January 21, 2025[f], the Applicant resubmitted a copy of the REMS Supporting Document including the proposed revisions. The Agency sent additional comments to the Applicant in the February 13, 2025 Information Request.

Most recently, on February 17, 2025[g], the Applicant addressed the Agency's comments from the February 13, 2025 Information Request and resubmitted a copy of the REMS Supporting Document, including the proposed revision to the Assessment Plan. This REMS Assessment Plan is the focus of this memo.

Conclusions and Recommendations

The Applicant accepted the revision of the proposed Stoboclo REMS Assessment Plan, from the Agency's Information Request dated February 13, 2025. We find the revision acceptable and have no further comment. The Assessment Plan is appended to this memo.

2 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] The May 28, 2024, REMS Review, available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8074806a.
[b] The February 13, 2025 information Request is available at:
[c] New BLA/Request for Review for BLA 761404, Stoboclo. Yeonsu-gu (South Korea): Celltrion Inc; 2023 Nov 30. Available from: \\CDSESUB1\EVSPROD\bla761404\0001\m1\us\
[d] New BLA/Request for Review for BLA 761404, Stoboclo. Yeonsu-gu (South Korea): Celltrion Inc; 2024 Apr 24. Available from: \\CDSESUB1\EVSPROD\bla761404\0011\m1
[e] The May, 30 2024 information request is available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807495fd
[f] The Applicant's January 21, 2025 "response to IR" is available from: \\CDSESUB1\EVSPROD\bla761404\0032\m1\us\
[g] The Applicant's February 18, 2025 "response to IR" is available from: \\CDSESUB1\EVSPROD\bla761404\0035\m1\

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REMS Assessment Plan Review MEMO

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)

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Application Type	BLA
Application Number	761404
Task Tracking Tool Number	2024-9234
Submission Type/Number	Original-1/33
Submission Date	January 21, 2025
Reviewer	Yanick Elame, PharmD
Team Lead	Kathryn Marwitz, PharmD, MPH
Associate Director	Page Crew, PharmD, MPH, BCPS
Review Completion Date	February 13, 2025
Non-Proprietary Name	Denosumab-bmwo
Proprietary Name	Stoboclo
Subject	Interim Comments for the Stoboclo Risk Evaluation and Mitigation Strategies (REMS) Assessment Plan
Applicant	Celltrion Inc.

1. Introduction

This memo is in reference to the proposed Risk Evaluation and Mitigation Strategy (REMS) Assessment Plan for the proposed Stoboclo REMS (hereafter, Stoboclo REMS). Refer to the May 28, 2024, REMS Review[a] for additional background information.

2. Background

On November 30, 2023, the Applicant submitted a 351(k) Biologics License Application (BLA) for a proposed (b) (4) biosimilar product to Prolia. The BLA included a proposed REMS that was comparable to the approved REMS for Prolia at the time (November 2023).[b]

On April 24, 2024[c], the Applicant resubmitted for review a REMS amendment that included a revised goal which was aligned with the goal for the Prolia REMS. The submission included a proposed REMS Assessment Plan, included within the REMS Supporting Document.

The Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) reviewed the proposed Assessment Plan and comments were sent to the Applicant on May 30, 2024[d].

Most recently, on January 21, 2025[e], the Applicant resubmitted a copy of the REMS Supporting Document including the proposed revisions to the Assessment Plan, and this REMS Assessment Plan is the focus of the memo.

3. Discussion

The Applicant accepted all of the proposed revisions from the Agency's Information Request dated May 30, 2024. However, the Applicant's REMS Assessment Plan included the following statement: "(b) (4) ", in lieu of the templated language provided by the Agency: "*The REMS Assessment Plan must include, but is not limited to, the following*" (underline added for emphasis.

To ensure that the Assessment Plan clearly outlines the metrics needed to inform REMS assessment, and that it is aligned with other REMS that mitigate similar risks, the Applicant will be asked to revise the introductory statement and resubmit the revised REMS Assessment Plan to the Agency. See section 5 below for comments to the Applicant

4. Conclusions and Recommendations

The proposed REMS Assessment Plan for Stoboclo, contained within the REMS Supporting Document requires revisions to ensure that it adequately informs REMS assessment.

We recommend sending the comments in **Section 5** below to the Applicant.

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[a] May 28, 2024, REMS Review, available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8074806a.

[b] New BLA/Request for Review for BLA 761404, Stoboclo. Yeonsu-gu (South Korea): Celltrion Inc; 2023 Nov 30. Available from: \\CDSESUB1\EVSPROD\bla761404\0001\m1\us\

[c] New BLA/Request for Review for BLA 761404, Stoboclo. Yeonsu-gu (South Korea): Celltrion Inc; 2024 Apr 24. Available from: \\CDSESUB1\EVSPROD\bla761404\0011\m1

[d] The May, 30 2024 information request is available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807495fd

[e] The Applicant's January 21, 2025 "response to IR" is available from: \\CDSESUB1\EVSPROD\bla761404\0032\m1\us\

5. Comments to the Applicant

We have the following comments regarding the proposed Stoboclo REMS Assessment Plan, submitted on January 21, 2025. The Stoboclo REMS Assessment Plan requires revisions to ensure that it adequately informs REMS assessment. Review of the proposed REMS is ongoing, and these comments should not be considered final.

REMS Assessment Plan

The Agency requires a revision to the REMS Assessment Plan as summarized below:

- Revise the introductory statement of your Assessment Plan and remove this statement: "(b) (4) ". Replace it with this statement, exactly as written: "The REMS Assessment Plan must include, but is not limited to, the following:"

Submit a copy of the revised REMS Assessment Plan within the REMS Supporting Document no later than 5pm EST on February 17, 2025 as a REMS correspondence. Do not submit your response as a REMS amendment.

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/s/

YANICK E ELAME
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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: 761404
Products: CT-P41 (denosumab-bmwo), injection,
APPLICANT: Celltrion LLC.
FROM: Marina Zemskova, M.D., Deputy Director for Safety]
DATE: 2/11/2025

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 CT-P41 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. CT-P41 is a (b) (4) 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. CT-P41 has the same mechanism(s) of action, route of administration, dosage form, strengths, and conditions of use as those of Prolia. Since CT-P41 shares the same mechanism of action (i.e., functions as a RANKL inhibitor), efficacy across indications is extrapolated for CT-P41. 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. CT-P41 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. CT-P41 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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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	761404
PDUFA Goal Date	February 28, 2025
Nexus TTT #	2023-7342
Reviewer Name(s)	Theresa Ng, PharmD, BCPS (DRM)
Team Leader	Yasmeen Abou-Sayed, PharmD (DRM)
Deputy Division Director	Laura Zendel, PharmD (DRM)
Review Completion Date	January 24, 2025
Subject	Addendum to the Evaluation of proposed REMS
Established Name	CT-P41 (denosumab-bmwo)
Trade Name	Stoboclo
Name of Applicant	Celltrion LLC
Therapeutic Class	Rank ligand 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 (SC) injection

This is an addendum to the Stoboclo REMS Review (Reference ID: 5471903) entered in DARRTS on October 31, 2024. On November 5, 2024, the Applicant submitted further drug manufacturing information, specifically, (b) (4) , which constitutes a major amendment to this application. The user fee goal date is extended to February 28, 2025. The information in the November 5, 2024 amendment does not affect the REMS and DRM's previous determination on the need for a REMS.

On January 20, 2025, Celltrion submitted a REMS amendment (eCTD seq no. 32) that incorporated the nonproprietary name, denosumab-bmwo and made other editorial revisions throughout the REMS document and REMS materials. DRM finds the proposed REMS received on January 20, 2025 acceptable and is appended to this review.

8 Page(s) of Draft REMS 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	761404
PDUFA Goal Date	November 30, 2024
Nexus TTT #	2023-7342
Reviewer Name(s)	Theresa Ng, PharmD, BCPS (DRM)
Team Leader	Yasmeen Abou-Sayed, PharmD (DRM)
Deputy Division Director	Laura Zendel, PharmD (DRM)
Review Completion Date	October 31, 2024
Subject	Evaluation of proposed REMS
Established Name	CT-P41 (denosumab-bmwo)
Trade Name	Stoboclo
Name of Applicant	Celltrion LLC
Therapeutic Class	Rank ligand 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 (SC) injection

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Stoboclo (CT-P411, denosumab – bmwo) Biologic Licensing Application (BLA) 761404 submitted by Celltrion Pharmaceuticals (Celltrion) as a (b) (4) biosimilar to the United States (US) licensed Prolia and Xgeva (denosumab), BLA 125320, under the proprietary names Stoboclo and Osenvelt, respectively on November 30, 2023. The proposed indications, presentations, and routes of administration for Stoboclo and Osenvelt, respectively, are the same as those approved for US-Prolia and US-Xgeva. The proposed indications for Stoboclo are for the treatment of those who are at high risk of fracture: (1) postmenopausal women with osteoporosis, (2) increase bone mass in men, (3) glucocorticoid-induced osteoporosis in men and women, (4) increase bone mass in men receiving androgen deprivation therapy for nonmetastatic prostate cancer, and (5) increase bone mass in women receiving adjuvant aromatase inhibitor therapy for breast cancer.

The clinical reviewers concluded that the comparative analytical and clinical studies demonstrated (b) (4) biosimilarity of CT-P411 and US-Prolia. There were no clinically meaningful differences in the efficacy and safety between CT-P41 and US Prolia. The safety profile for Stoboclo is expected to be similar to that for US-Prolia. (b) (4), (b) (5)

Prolia was approved with a REMS to mitigate the risks of hypocalcemia, osteonecrosis of the jaw, atypical femur fracture, serious infections, and dermatological reactions. A REMS for Xgeva is not required because of the differences in benefit-risk profiles of the population for Xgeva versus Prolia. This review will focus on the proposed REMS for Stoboclo referencing Prolia. On March 5, 2024, a modification to the Prolia REMS was approved that updated the risk messages in the REMS with the safety labeling change (e.g., a boxed warning for severe hypocalcemia in patients with advanced chronic kidney disease and risk messages), removed the other four risks from the REMS, and removed the medication guide as an element of the REMS.

Due to the REMS modifications approved for the Prolia REMS on March 5, 2024, the Agency informed Celltrion on March 26, 2024 to update their REMS proposal for Stoboclo to align with the approved changes to the Prolia REMS. Celltrion submitted REMS amendments on April 24, 2024 and August 6, 2024 in response to the Agency's comments.

DRM recommends approval of the Stoboclo REMS. The elements of the Stoboclo REMS are the same for the currently approved Prolia REMS and consist of a communication plan and timetable for submission of assessments. There are no significant operational or implementation differences. The Stoboclo REMS is designed to communicate the same key risk messages and achieve the same level of patient safety as the Prolia REMS. In addition, the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) found the REMS Assessment Plan as submitted on August 6, 2024 to be acceptable.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Stoboclo (CT-P41, denosumab-bmwo). Celltrion Inc. submitted a Biologic Licensing Application (BLA) 761404 for CT-P41 under proprietary names Stoboclo and Osenvelt as (b) (4) biosimilar products to United States (US) approved Prolia and Xgeva, respectively, licensed by Amgen under BLA 125320, as the reference listed drug (RLD) in the application. Celltrion proposes the same indications for CT-P41 as US-Prolia and US-Xgeva, respectively.

On November 30, 2023, Celltrion submitted a BLA with a proposed REMS for Stoboclo that initially consisted of a MG, CP, and timetable for submission of assessment. Due to the REMS modifications approved for the Prolia REMS on March 5, 2024[1], the Agency informed Celltrion on March 26, 2024 to update their REMS proposal for Stoboclo to align with the March 5, 2024 approved changes with the Prolia REMS. Celltrion submitted a REMS amendment on April 24, 2024 in response to the Agency's March 26, 2024 information request (IR). Further edits to the REMS were submitted by the Applicant on August 6, 2024 as requested in the Agency's July 31, 2024 IR. The updated Stoboclo REMS consists of a communication plan (CP) and a timetable for submission of assessments and is the focus of this review.

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 (denosumab-bbdz) under BLA 761362 with proprietary names Jubbonti (60 mg/1 mL in a pre-filled syringe or PFS) and Wyost (120 mg/ 1.7 ml or 70 mg/mL in a single-dose vial), approved on March 5, 2024.[2] Celltrion developed CT-P41 (denosumab-bmwo) under proprietary names Stoboclo and Osenvelt as (b) (4) biosimilars to US-Prolia and US-Xgeva, respectively. CT-P41 is under review in the Division of General Endocrinology (DGE) under the 351(K) pathway. Celltrion proposed the same indications, dosages, and presentations for CT-P41 under Stoboclo and Osenvelt to US-Prolia and US-Xgeva, respectively.

The proposed indications for Stoboclo are:

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 recommended dose for Stoboclo is 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).

The proposed indications for Osenvelt are:

1) Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors,
2) Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity, and
3) Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

The recommended dose for Osenvelt is 120 mg subcutaneous (SC) injection every four weeks. For giant cell tumor of bone and hypercalcemia of malignancy indications, an additional 120 mg dose on Days 8 and 15 of the first month of therapy are recommended.

2.2. Prolia REMS

Prolia was approved with a REMS in 2010 to mitigate the risk of osteonecrosis of the jaw, serious infection, and dermatologic reactions. The Prolia REMS has been modified multiple times over the years to add the risks of hypocalcemia and atypical femur fracture to be mitigated by the REMS. The last major modification on March 5, 2024 updated the REMS goal and streamlined the REMS materials to align with the approval of a safety labeling change (SLC).[1,3] See Table 1 below.

Table 1. Summary of the Approved Prolia REMS (March 5, 2024)

REMS Goal
The goal of the Prolia REMS is to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Prolia. Objective 1: 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
CP and timetable for submission of assessments (18- months, 3, and 7 years from date of REMS modification approval, March 5, 2024).
CP materials
• REMS Letter to Healthcare Providers • REMS Letter to Professional Societies • Patient Guide • REMS website

2.3. Regulatory History

The following is a summary of the regulatory history for BLA 761404 relevant to this review:

- 11/30/2023: BLA 761404 submitted under the 351(K) regulatory pathway as (b) (4) biosimilar denosumab biological product to US-licensed Prolia and US-licensed Xgeva with the same respective indications, dosages, and presentations.
- 3/5/2024: Prolia S-217 REMS modification approved. 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.
- 3/26/2024: The Agency issued an Information Request (IR) for Celltrion to update and align the REMS proposal with the Prolia REMS modification approved March 5, 2024.
- 4/24/2024: The Applicant submitted a REMS amendment in response to the Agency's March 26, 2024 IR (eCTD seq no. 11).
- 5/30/2024: The Agency issued an IR for Celltrion to incorporate editorial changes in the REMS Document and Patient Guide. In addition, the Agency requested the Applicant to incorporate in the REMS Supporting Document: information on undeliverable and unopened REMS Letters to HCPs and professional societies in REMS Document, suggested key risk messages and key performance indicators, and edits to the REMS Assessment Plan.
- 6/7/2024: Celltrion submitted a REMS amendment in response to the Agency's May 30, 2024 IR (eCTD seq. no. 15).
- 7/31/2024: The Agency issued an IR for Celltrion to incorporate further editorial changes to correct minor grammatical errors and eliminate redundancies.
- 8/6/2024: Celltrion submitted a REMS amendment in response to the Agency's July 31, 2024 IR (eCTD seq. no. 23).
- 8/19/2024: The Agency issued an Advice Letter informing Celltrion of the conditionally acceptable determination for their proposed product nonproprietary name, denosumab-bmwo.

3. Benefit Assessment

The Applicant submitted two studies, a comparative analytical study (CT-P41 1.2, NCT06037395) and a comparative clinical study (CT-P41 3.1, NCT04757376), in support of the biosimilarity of CT-P41 to US-Prolia.

Study CT-P41 1.2 (Study 1.2) is a Phase 1, randomized, double-blind, two-arm, parallel group, single-dose study to compare pharmacokinetic (PK), pharmacodynamic (PD) and safety of two formulations of denosumab (CT-P41 and US-Prolia) in healthy male subjects. There were 149 subjects (74 in the CT-P41 cohort and 75 in the US-Prolia cohort) between the ages of 28 and 55 years who completed the study.

Overall demographics and baseline characteristics were similar between the two treatment groups. PK similarity between CT-P41 and US-Prolia was demonstrated since the 90% confidence intervals (CIs) for the ratio for CT-P41/US-Prolia of geometric means for area under the curve (AUC) of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and maximum serum concentration (C_{max}) were all completely contained within the pre-specified equivalence limits [0.80; 1.25]. PD profiles for both bone turnover biomarkers, s-CTX[b] and P1NP[c] are similar between CT-P41 and US- Prolia and provided further support for the biosimilarity between these two products.

Study CT-P41 3.1 (Study 3.1) is a Phase 3, multicenter, randomized, double-blind, active-controlled study to compare efficacy, PK, PD, and safety of CT-P411 and US-Prolia in postmenopausal women with osteoporosis. The study duration was 78 weeks. A total of 479 female subjects were randomized in a 1:1 ratio to receive two doses of either 60 mg of CT-P411 (240 subjects) or US-Prolia (239 subjects) on Day 1 and at Week 26 (treatment period I or TP1). At week 52 (treatment period 2 or TP2), subjects who received US-Prolia during TP1 were re-randomized in a 1:1 ratio to either continue on US- Prolia 60 mg or switch to CT-P411. Subjects who received CT-P411 in TP1 continued with CT-P411. All participants received daily supplementation of 1000 mg elemental calcium and at least 400 IU vitamin D. The patient demographics and baseline disease characteristics were balanced between the treatment groups. The primary comparative efficacy endpoint of percent change from baseline in bone mineral density (BMD) for lumbar spine (L1 to L4) at 52 weeks in the intent to treat population between the two treatment groups was -0.19 (90% CI: -0.76, 0.38) and was within the pre-specified margin (-1.45%, 1.45%). PK analysis showed similar mean denosumab concentration-time profiles between CT-P41 and US-Prolia for Treatment Period 1 and Treatment Period 2. PD assessment with bone turnover biomarkers s-CTX and P1NP were considered exploratory and were similar between CT-P41 and US-Prolia treatment groups in both treatment periods I and II.

The incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) was similar between treatment groups in Studies CT-P41 1.2 and CT-P41 3.1 and the incidence of NAbs was low in all treatment groups in both studies.

Based on the results from Studies 1.2 and 1.3, the clinical reviewer concluded that biosimilarity was demonstrated between CT-P411 and US-Prolia CT.[d]

4. Risk Assessment & Safe-Use Conditions

The evaluation of safety is based primarily on the comparative clinical study in post-menopausal women with osteoporosis (Study 3.1) with additive supportive safety data from the comparative clinical

[b] s-CTX: serum C-terminal telopeptide of type I collagen

[c] P1NP: Procollagen type 1 N-terminal propeptide

[d] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

pharmacology study (Study 1.1), in healthy adult males. The clinical reviewer determined the size of the safety database is adequate to make a determination of clinical similarity between CT-P41 and US-Prolia.

There were two deaths reported in Study 3.1, both in subjects receiving CT-P31. None were attributed to study drug (one from progression of ovarian cancer, the other from coronary artery disease). No deaths occurred in comparative PK Study 1.2.

In Study 3.1, during treatment period I, serious treatment emergent adverse events (TEAEs) occurred in 7 (3%) and 10 (4%) patients on CT-P41 and US-Prolia, respectively. There was one serious adverse event (SAE) of fracture (preferred term *humerus fracture)* in a subject assigned to US-Prolia. TEAEs occurring in >5% of subjects and more frequently in Prolia compared to placebo were back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. During treatment period 2, serious adverse events (SAEs) occurred in 8 (4%), 2 (2%) and 0 subjects in the CT-P41 maintenance, US-Prolia maintenance and switch to CT-P41 groups, respectively. The clinical reviewer determined that there was no clinically meaningful difference in either the nature or frequency of SAEs between CT-P41 and US-Prolia or following a switch from US-Prolia to CT-P41 compared to US-Prolia maintenance.[e] The nature of adverse events was similar between treatment groups and consistent with the known safety profile of denosumab. Small numeric differences in actual incidence (for example, UTI) between groups is likely due to chance rather than inherent differences in study drug.

Immunogenicity data (see Section 4 above) also support that CT-P41 has no clinically meaningful differences from US-Prolia.

4.1. Hypocalcemia

Hypocalcemia especially in patients with bone-mineral disorder is a known risk for denosumab and this risk is highlighted in the US-Prolia PI as a boxed warning. The Applicant assessed for hypocalcemia during which calcium nadir is anticipated (within the first 2 weeks following study drug injection). In Study 3.1, there were no meaningful differences between treatment groups in median change in chemistry or hematology parameters over time during treatment period 1.

5. Expected Postmarket Use

Stoboclo is expected to be administered by a healthcare provider in an outpatient clinic setting. The patient and prescriber population for Stoboclo are expected to be similar to that of Prolia. The majority of prescribers for Stoboclo will likely be primary care providers, endocrinologists, rheumatologists, and gynecologists involved in the treatment of patients with osteoporosis. Due to the increased risk of severe hypocalcemia, patients with advanced chronic kidney disease may warrant further evaluation by nephrology specialists to ensure appropriateness of therapy with Stoboclo.

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

6. Review of the Proposed REMS

Because of the SLC approved on January 19, 2024 and subsequent REMS modification to US-Prolia on March 5, 2024, the Agency advised Celltrion to update their REMS proposal to align with risk message changes in the Prolia labeling and REMS in the March 26, 2024 IR.

The proposed REMS submitted by Celltrion on August 6, 2024 includes the following REMS elements: a communication plan and timetable for submission of assessments.

6.1. REMS Document

Celltrion submitted a REMS Document that is comparable to the most recently approved Prolia REMS, and the REMS content is consistent with the recommendations in the Format and Content of a REMS Document Guidance for Industry and the REMS Document Technical Conformance Guide.

Reviewer Comments: *DRM finds the REMS Document acceptable.*

6.2. REMS Goals

Celltrion proposed the following REMS goal for Stoboclo:

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

Objective 1: 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 Stoboclo in patients with advanced chronic kidney disease

Reviewer's Comments: *DRM finds the REMS goal and objective statements as stated above for Stoboclo acceptable. The REMS goal for Stoboclo aligns with the REMS goal for Prolia, the reference listed drug.*

6.3. Communication Plan

Celltrion proposed a communication plan (CP) consisting of the following materials:

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

The Stoboclo REMS CP materials have the same content and risk messages as in the Prolia REMS.

Reviewer's Comments: *We find the communication plan materials comparable to the Prolia REMS and therefore acceptable.*

6.3.1. Dissemination Plan

Celltrion proposed the same dissemination plan for the **REMS Letter to Healthcare Providers** and the **REMS Letters to Professional Societies** as in the Prolia REMS.

Similarly, the **Patient Guide** along with the prescribing information (PI) will be disseminated at professional meetings where Celltrion has a presence, and through field-based sales and by medical representatives during discussions with healthcare providers from the date Stoboclo is first commercially distributed for the duration of the REMS.

Additionally, the REMS materials will be accessible through the Stoboclo REMS website for the duration of the REMS.

Reviewer's Comments: *DRM finds the dissemination plan acceptable. It is comparable to the Prolia REMS.*

6.4. Timetable for Submission of Assessments

Celltrion proposed a timeline for REMS assessments at 18-months, 3-years, and 7-years from the date of the initial approval of the REMS.

Reviewer's Comments: *DRM and the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) agree with Celltrion's proposed timetable for submission of assessments.*

6.5. REMS Supporting Document

The REMS Supporting Document contains the REMS program background information and a description of the operations of the REMS. Celltrion provided information in the supporting document detailing the distribution plan for the communication plan materials and included contingencies for undeliverable mail and email. The targeted audience for the **REMS Letter to Healthcare Providers** and **REMS Letters to Professional Societies** is the same prescriber population and professional societies as the Prolia REMS. In addition, Celltrion incorporated the Key Risk Messages (KRMs) and Key Performance Indicators (KPIs) from the Agency's May 30 , 2024 IR which are the same as in the Prolia REMS.[4]

Reviewer's Comments: *DRM finds the information in the REMS supporting document acceptable. The information in the REMS Supporting Document aligns with the REMS Document and REMS materials. The contingency plan for undeliverable mails and emails is comparable to the Prolia REMS*

6.5.1. Key Risk Messages (KRMs)

Celltrion incorporated the Key Risk Messages (KRMs) for healthcare providers and patients from the Agency's May 30, 2024 IR and are described below.

Based on the objectives, the KRMs of the Stoboclo REMS for healthcare providers included in the **REMS Letter to Healthcare Provider** and **REMS Letter to Professional Societies** are:

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

Based on the objectives, the KRM of the Stoboclo REMS for patients included in the **Patient Guide** is:

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

Reviewer's Comments: *The KRMs in the REMS letters and Patient Guide are acceptable. They are similar to the KRMs in the Prolia REMS. KRMs identify the most critical information for stakeholders to know about the risk and safe use behaviors to mitigate the risk. The KRMs are based on the proposed REMS goals and objectives and guide the messaging throughout the REMS materials. The KRMs align with the serious risk highlighted in the Boxed Warning and Warnings and Precautions section of the PI.*

6.5.1.1. Key Performance Indicator (KPI) and Targeted Threshold

Celltrion incorporated the KPIs from the Agency's May 30, 2024 IR. The KPI and associated targeted threshold for the Stoboclo REMS are described below.

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 CKD-MBD before initiating Stoboclo	% 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 Stoboclo	≥ 80% targeted knowledge threshold

Reviewer's Comments: *DRM and DMAMES agree with the Stoboclo REMS KPI and targeted threshold. The KPI for Stoboclo REMS is similar to the Prolia REMS. KPIs are measures essential in determining whether the REMS is functioning as designed and the targeted thresholds help assess whether the REMS is meeting the objectives or whether further evaluation or changes to the REMS are warranted. Per the 2019 FDA Draft Guidance: Survey Methodologies to Assess REMS Goals That Relate to Knowledge Guidance, for assessments involving stakeholder knowledge surveys (e.g., for REMS with a Communication Plan), 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 key message domain. KPIs at or above the target threshold 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 knowledge threshold may change with more experience with the REMS and accumulation of postmarket data.

6.5.2. REMS Assessment Plan

Celltrion updated the assessment plan to align with the changes requested in the Agency's May 30, 2024 IR.[4,5]

Reviewer's Comments: *DRM and DMAMES find the Assessment Plan acceptable. The Assessment Plan is appended to this review.*

7. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Stoboclo (denosumab–bmwo) on the basis of the efficacy and safety information currently available. (b) (4), (b) (5) .

CT-P-41 is proposed as (b) (4) biosimilar to denosumab approved as US licensed Prolia under BLA 125320 by Amgen. The Applicant submitted a BLA for CT-P41 under proprietary name Stoboclo for the same proposed indications, dosages, and presentation as US-Prolia. The clinical review team (DGE, and Office of Therapeutic Biologics and Biosimilars [OTBB]) determined the Applicant demonstrated that CT-P41 is biosimilar (b) (4) to US-Prolia. The primary endpoints for both Studies 1.2 and 1.3 were well within the prespecified limits and there were low and similar incidences of ADAs and Nab in both studies. The clinical review team determined the Applicant provided sufficient justification that CT-P41 can be expected to produce the same clinical result as US-Prolia in any given patient. The safety profile of CT-P41 is consistent with the known safety profile of denosumab and the clinical review team concluded that there were no clinical meaningful differences in efficacy and safety between CT-P41 and US Prolia.

Similar to Prolia, Stoboclo will be required to have a REMS to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease, including dialysis-dependent patients. The proposed Stoboclo REMS is comparable to the Prolia REMS consisting of a communication plan and timetable to submission of assessments. The REMS document, communication plan materials (i.e., **Patient Guide, REMS letter for Healthcare Providers, REMS letter for Professional Societies**, and **REMS website**), and REMS Supporting document detailing the operations and distribution plan for the materials are similar to the Prolia REMS. The Stoboclo REMS will communicate the same key risk messages and achieve the same level of patient safety as the Prolia REMS. We acknowledge that addition of a different REMS for denosumab products may introduce some burden on the healthcare system, however, we have determined this is acceptable as it is expected to be minimal and will be outweighed by the advantage of having additional biosimilar denosumab product available for patients.

8. Conclusion & Recommendations

DRM finds the proposed REMS received on August 6, 2024 acceptable and is appended to this review.

9. Appendices

(b) (4)

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/s/

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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	761404
PDUFA Goal Date	November 30, 2024
Nexus TTT#	2023-7342
Reviewer Names	Theresa Ng, PharmD, BCPS Katherine Hyatt Hawkins Shaw, PhD
Team Leaders	Yasmeen Abou-Sayed, PharmD
Deputy Division Director	Laura Zendel, PharmD
Review Completion Date	July 30, 2024
Subject	Interim Review of proposed REMS
Established Name	CT-P41 (denosumab-XXXX)
Trade Name	Stoboclo
Name of Applicant	Celltrion, LLC
Therapeutic Class	Rank ligand inhibitor
Formulation(s)	60 mg per 1 ml solution in a single-dose prefilled syringe
Dosing Regimen	60 mg every 6 months as a subcutaneous (SC) 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 Stoboclo, Biological Licensing Application (BLA) 761362, submitted by Celltrion LLC on November 30, 2023 and amended on April 24, 2024 and June 7, 2024. Stoboclo is a rank ligand inhibitor intended as (b) (4) (b) (4) biosimilar denosumab product with the same proposed indications to the reference biologic product Prolia licensed under BLA 125320 by Amgen Inc.

The proposed indications for Stoboclo are:

- 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 at 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

This application is submitted for review under the 351(K) BLA regulatory pathway in the Division of General Endocrinology (DGE).

Prolia is approved with a REMS to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease, including dialysis-dependent patients. Celltrion proposed a separate REMS for Stoboclo consisting of a communication plan (CP) and timetable for submission of assessments. The communication plan materials proposed in the Stoboclo REMS are similar to the Prolia REMS.

This interim review discusses DRM comments on the REMS proposal for Stoboclo submitted by the Applicant on June 7, 2024.

2. Regulatory History

- 11/30/2023: BLA 761404, CT-P41 (denosumab-XXXX) submitted under the 351(K) regulatory pathway as a biosimilar (b) (4) denosumab biological product to US-licensed Prolia and US-licensed Xgeva with the same respective indications, dosages, and presentations.
- 3/5/2024: Prolia S-217 REMS modification approved. The REMS modification included revising the risk mitigated by the REMS to "the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients", removing the risks of atypical femur fracture (AFF), osteonecrosis of the jaw (ONJ), serious infections, and dermatologic reactions from the REMS, and removing the medication guide (MG) as an element of the REMS. The REMS modification also included changes to the appended REMS materials and risk messages in the REMS materials to align the with the new safety information in the prescribing information (PI) and additional timetable for submission of assessment of 18-months, 3-years and 7- years.
- 3/26/2024: The Agency issued an Information Request (IR) to Celltrion to update and align the REMS proposal with the recent changes to the Prolia REMS.
- 4/24/2024: The Applicant submitted a REMS amendment in response to the Agency's March 26, 2024 IR (eCTD seq no. 11).

- 5/30/2024: The Agency issued an IR to Celltrion with further edits to the REMS Document and Patient Guide. Additionally, the Agency provided information on Key Risk Messages and Key Performance Indicators to be included in the REMS Supporting Document and edits to the Assessment Plan.

- 6/7/2024: Celltrion submitted a REMS amendment in response to the Agency's May 30, 2024 IR (eCTD seq. no. 15).

3. Conclusions and Recommendations

DRM does not find the proposed REMS for Stoboclo (denosumab biologic product) as submitted on June 7, 2024, to be acceptable. Further changes to the REMS Document, Patient Guide, REMS website, and REMS Supporting Document are necessary for consistency and to reduce redundant information. See Section 4 below for details.

4. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on June 7, 2024. Review of the REMS proposal is ongoing; these comments should not be considered final.

REMS Document

- See redlined REMS Document with edits for consistency with the REMS Document Technical Conformance Guide.

Communication Plan (CP) materials

REMS Letters for Healthcare Providers and REMS Letter for Professional Societies

- Provide the name and URL to the REMS website to replace the placeholder that currently has the following language, "<link to the Stoboclo REMS will be provided upon approval>". This must be included for approval.

Patient Guide

- Bold the final line of the guide that alerts patients that they may need an expert on CKD-MBD for emphasis.

REMS website

- Pages 3-5 of the REMS website (PDF version) appear to repeat the information from pages 1-2. Remove redundant content. If pages 3-5 of the REMS website (PDF version) are meant to represent the mobile version of the REMS website, you should include the mobile version as an appendix to the REMS Supporting Document.

REMS Supporting Document

- Incorporate edits for consistency in the REMS Supporting Document. See redlined document.

(b) (4)

(b) (4)

Submit the following revised REMS materials by **COB August 6, 2024.** 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:

The Agency requests that you submit the REMS documents as shown below:

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

3 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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LAURA A ZENDEL
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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)

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The proposed indications for Stoboclo are:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture
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- 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

This application is submitted for review under the 351(K) BLA regulatory pathway in the Division of General Endocrinology (DGE).

Prolia is approved with a REMS to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease, including dialysis-dependent patients. Celltrion proposed a separate REMS for Stoboclo consisting of a communication plan (CP) and timetable for submission of assessments. The communication plan materials proposed in the Stoboclo REMS are similar to the Prolia REMS.

This interim review discusses DRM and Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)[1] initial comments on the REMS proposal for Stoboclo submitted by the Applicant on April 24, 2024.

2. Regulatory History

- 11/30/2023: BLA 761404, CT-P41 (denosumab-XXXX) submitted under the 351(K) regulatory pathway as a biosimilar (b) (4) denosumab biological product to US-licensed Prolia and US-licensed Xgeva with the same respective indications, dosages, and presentations.
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- 3/26/2024: The Agency issued an Information Request (IR) for Celltrion to update and align the REMS proposal with the recent changes to the Prolia REMS.
- 4/24/2024: The Applicant submitted a REMS amendment in response to the Agency's March 26, 2024 IR (eCTD seq no. 11).

3. Review of Applicant's Proposed REMS

Celltrion submitted a comparable REMS to the currently approved Prolia REMS, with editorial differences related to the proprietary name of the denosumab product identified as "Stoboclo" and Celltrion as the marketing sponsor. Celltrion proposed a REMS consisting of a Communication Plan (CP) and timetable for submission of assessment. The Communication Plan materials consist of:

- REMS Letter to Healthcare Providers,
- REMS Letter to Professional Society,
- Patient Guide, and
- REMS website.

4. Conclusions and Recommendations

DRM and DMAMES do not find the proposed REMS for Stoboclo (denosumab biologic product) as submitted on April 24, 2024, to be acceptable. Further changes to the REMS Document, REMS Supporting Document and REMS materials are needed for consistency with the currently approved Prolia REMS. See Section 5 below for details.

5. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on April 24, 2024. Review of the REMS proposal is ongoing; these comments should not be considered final.

General Comments

- Ensure that all font styles used across all materials are a sans serif font to increase readability.

REMS Document

- See redlined REMS Document with edits for consistency with the *REMS Document Technical Conformance Guide*.

Communication Plan (CP) materials

Patient Guide

- Call attention to "call your doctor right away if you think you may be having any of these symptoms," by either adding a box to outline the text or by increasing the font size.

REMS Supporting Document

The REMS Supporting Document should contain the background and rationale for the denosumab REMS, description of the stakeholder responsibilities, how they carry out those responsibilities, and how the REMS will be implemented.

- Include information on actions to be taken for undeliverable mails and emails to healthcare providers and professional societies, and responsibilities of the sales force liaisons in providing the Patient Guide during office visits to ensure the information in the REMS Supporting Document is consistent with the requirements in the REMS Document (see comments in redlined document).
- Include new sections for Key Risk Messages (KRMs) and Key Performance Indicators (KPIs).

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

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

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)

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 (see redlined 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 Stoboclo	% 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 Stoboclo	≥ 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.

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

The Agency requires revisions to the REMS Assessment Plan. The changes are summarized. below, and a copy of the Assessment Plan is included, with additions underlined and deletions in ~~strikethrough~~.

1. A metric was added (Evaluation of Healthcare Providers' Knowledge) to assess stakeholder understanding of the serious risks associated with, and the safe use of Stoboclo. This is required to evaluate the objective of the REMS; "Inform healthcare providers."

   Furthermore, we refer you to the FDA draft guidance*: REMS Assessment: Planning and Reporting Guidance for Industry* (2019) and to the FDA draft guidance: *Survey Methodologies to Assess REMS Goals That Relate to Knowledge Guidance for Industry* (2019). Section 505-1(g)(3) of the FD&C Act specifies that a "REMS assessment shall include, with respect to each goal in the strategy, an assessment of the extent to which the approved strategy, including the elements, is meeting the goal or whether the goal or elements should be modified."

   Because the goal of your proposed REMS is knowledge based, a survey to evaluate stakeholders' understanding of the serious risk associated with Stoboclo use will serve as an important tool to assess whether the REMS is meeting its goal.

2. Metric #6, Overall Assessment of REMS Effectiveness, was revised to align with that of the Assessment Plans of previously approved REMS for similar products.

Submit the following revised REMS materials by **COB June 7, 2024.** 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:

The Agency requests that you submit the REMS documents as shown below:

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

6	Patient Brochure	Tracked MS Word, Clean MS Word, PDF
8	REMS Website Screenshots	PDF
9	Compiled REMS Document (consisting of REMS Document and appended REMS materials)	PDF

6. References

1. Elame Y. DMAMES. REMS Assessment Plan Review, dated may 28, 2024.

3 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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REMS Assessment Plan Review

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)

*****This document may contain information that cannot be released to the public*****

Application Type	BLA
Application Number	761404
Task Tracking Tool Number	2024-9234
Submission Type/Number	Original-1/12
Submission Date	April 24, 2024
Reviewer	Yanick Elame, PharmD
Team Lead	Page Crew, PharmD, MPH, BCPS (DMAMES)
Associate Director Designee	Joseph Paradis, PharmD (OMEPRM)
Review Completion Date	May 28, 2024
Non-Proprietary Name	Denosumab
Proprietary Name	Stoboclo
Subject	Interim Comments for the Stoboclo Risk Evaluation and Mitigation Strategies (REMS) Assessment Plan
Applicant	Celltrion Inc.
Therapeutic Class	RANK ligand (RANKL) inhibitor
Dosage Form and Strength	60 mg per 1 mL solution in a single-dose prefilled syringe, for subcutaneous injection

1. Introduction

This review is in reference to the proposed Risk Evaluation and Mitigation Strategy (REMS) Assessment Plan for the proposed Stoboclo REMS (hereafter, Stoboclo REMS).

Stoboclo is a RANK ligand (RANKL) inhibitor proposed as a biosimilar to the reference product, Prolia (approved under Biologics License Application 125320 by Amgen Inc.).[a] Prolia has an approved REMS that includes a Communication Plan, and a Timetable for Submission of Assessments.[b] The proposed indications for Stoboclo are the same as those for Prolia:

- 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 at high-risk 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.

2. Background

On November 30, 2023, the Applicant submitted a 351(k) Biologics License Application (BLA) for a proposed (b) (4) biosimilar product to Prolia. The BLA included a proposed REMS that was comparable to the approved REMS for Prolia at the time (November 2023).[c]

On March 5, 2024, the REMS for the reference drug, Prolia, was modified to maintain the Medication Guide as part of approved labeling, but not as an element of the approved REMS, along with other modifications outlined in a January 19 2024[d] REMS Modification Notification Letter. The Stoboclo Applicant was notified on March 26, 2024,[e] in an Information Request (IR), to realign their proposed REMS with the modified Prolia REMS.

On April 24, 2024, the Applicant resubmitted for review a REMS amendment that included a revised goal which is aligned with the new goal for the Prolia REMS. The submission also includes a proposed REMS Assessment Plan, included within the REMS Supporting Document.

2.1 REMS Goal, Elements, and Timetable for Submission of Assessments

Goal

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

Objective 1: Inform healthcare providers on:

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[a] REMS/Response to IR, BLA 761404, Stoboclo. Yeonsu-gu (South Korea): Celltrion Inc; 2024 APR 24. Available from available at: \\CDSESUB1\EVSPROD\bla761404\0011\m1\us\draft-rems-supporting-document.pdf

[b] Hanan, E. Approval Letter. Silver Spring (MD): FDA, CDER, DGE, (US); 2024 MAR 05. BLA 125320. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8072dc62

[c] New BLA/Request for Review for BLA 761404, Stoboclo. Yeonsu-gu (South Korea): Celltrion Inc; 2023 Nov 30. Available from: \\CDSESUB1\EVSPROD\bla761404\0001\m1\us\

[d] Hanan, E. REMS Modification Notification. Silver Spring (MD): FDA, CDER, DGE, (US); 2024 JAN 19. BLA 125320. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8071d7fb

[e] Smith, D. Information Request. Silver Spring (MD): FDA, CDER, DGE, (US); 2024 MAR 26. BLA 761404. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80734b7b

- 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 Stoboclo, in patients with advanced chronic kidney disease.

Elements
The proposed Stoboclo REMS, like that of the reference drug Prolia, is a Communication Plan only REMS.

Timetable for Submission of Assessments:
The proposed timetable for submission of assessments is at 18 months, 3 years, and 7 years from the date of the initial REMS approval.

3. Review of the Stoboclo REMS Assessment Plan

The proposed Stoboclo REMS Assessment Plan is contained within the REMS Supporting Document (RSD) and is available at:

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The Applicant intends to disseminate REMS communication materials (REMS letters, and a Patient Guide) to different stakeholders according to a prespecified timetable. The Assessment Plan includes several metrics grouped under the following three Assessment Categories:

1. *Program Outreach and Communication:*

   This section contains metrics that track launch of the Communication Plan including the number/type of letters sent to different stakeholders. It also contains metrics assessing distribution of the Patient Guide, and display/distribution of Stoboclo REMS materials at scientific meetings.

2. *Program Implementation and Operations:*

   This section contains metrics that track the implementation and operationalization of the REMS such as the date of commercial availability and launch of the website (including website traffic). The section also reports Stoboclo utilization data, stratified by indication and healthcare provider (HCP) specialty.

3. *Health Outcomes and/or Surrogates of Health Outcomes*

   This section contains metrics that report on a summary/analysis of all post-marketing reports of severe hypocalcemia associated with Stoboclo.

(b) (4)

(b) (4)

Overall, the proposed Assessment Plan is similar to that of the reference drug, (b) (4)

4. Discussion

On November 7, 2023,[f] a Safety Labeling Change Notification was issued to Amgen, holder of the BLA for the reference drug Prolia. The Safety Labeling Change Notification indicated the following: "Since Prolia was approved on June 1, 2010, we have become aware of post-marketing reports of severe hypocalcemia in patients with advanced chronic kidney disease including dialysis-dependent patients. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA." The Safety Labeling Change Notification required Amgen to revise the labeling and add a "Boxed Warning" in the Prolia labeling to warn against the risk of severe hypocalcemia in patients with advanced kidney disease.

On January 19, 2024,[g] a labelling change incorporating the required labeling revisions and inclusion of the 'Boxed Warning" was approved for Prolia, and the Prolia REMS was subsequently modified on March 5, 2024[b]. As part of the modification, the goal of the Prolia REMS was revised and the risk of hypocalcemia was further defined. The objective of the Prolia REMS to inform healthcare providers was revised from: "Risk of severe hypocalcemia with advanced chronic kidney disease" to, "Risk of severe hypocalcemia with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m2)." The timetable for submission of assessments of the REMS was also revised to include submission of assessments at 18 months, 3 years, and 7 years following approval of the modified REMS on March 5, 2024.

Section 505-1(g)(3) of the Federal Drug and Cosmetic Act specifies that a "REMS assessment shall include, with respect to each goal in the strategy, an assessment of the extent to which the approved strategy, including the elements, is meeting the goal or whether the goal or elements should be modified."

In addition, per the FDA draft guidance, *REMS Assessment: Planning and Reporting Guidance for Industry*,[h] "When a REMS includes an objective to inform or educate patients or health care professionals about a serious risk associated with a drug, or about the safe use of a drug, the assessment

[f] Hanan, E. Labeling Supplement Request. Silver Spring (MD): FDA, CDER, DGE, (US); 2023 NOV 07. BLA 125320. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80706dbb

[g] Hanan, E. Approval Letter. Silver Spring (MD): FDA, CDER, DGE, (US); 2024 JAN 19. BLA 125320. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8071da96

[h] Draft Guidance for Industry: REMS Assessment: Planning and Reporting. 2019. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rems-assessment-planning-and-reporting

plan should include an assessment of these stakeholders' knowledge." Also, as mentioned in the FDA draft guidance: *Survey Methodologies to Assess REMS Goals That Relate to Knowledge Guidance for Industry,*[i] for REMS with goals related to knowledge, "the REMS assessment plan generally includes, as appropriate, a survey to evaluate patients' and healthcare providers' understanding of the serious risks associated with, and safe use of, the drug."

(b) (4)

As part of the Prolia REMS modification, the Prolia REMS is now required to submit assessments which include knowledge surveys.

5. Conclusions and Recommendations

The proposed REMS Assessment Plan for Stoboclo, contained within the REMS Supporting Document requires further revisions to align with that of the reference drug and other REMS designed to mitigate similar risks.

We recommend sending the comments in **Section 6** and the revised Assessment Plan to the Applicant.

6. Comments to the Applicant

We have the following comments regarding the proposed Stoboclo REMS Assessment Plan, submitted on April 24, 2024. The Stoboclo REMS Assessment Plan requires revisions to inform the objective of the REMS and align with previously approved REMS for similar products. Review of the proposed REMS is ongoing, and these comments should not be considered final.

REMS Assessment Plan

The Agency requires revisions to the REMS Assessment Plan. The changes are summarized. below, and a copy of the Assessment Plan is included, with additions underlined and deletions in ~~strikethrough~~.

1. A metric was added (Evaluation of Healthcare Providers' Knowledge) to assess stakeholder understanding of the serious risks associated with, and the safe use of Stoboclo. This is required to evaluate the objective of the REMS; "Inform healthcare providers."

   Furthermore, we refer you to the FDA draft guidance*: REMS Assessment: Planning and Reporting Guidance for Industry* (2019) and to the FDA draft guidance: *Survey Methodologies to Assess REMS Goals That Relate to Knowledge Guidance for Industry* (2019). Section 505-1(g)(3) of the FD&C Act specifies that a "REMS assessment shall include, with respect to each goal in the strategy, an assessment of the extent to which the approved strategy, including the elements, is meeting the goal or whether the goal or elements should be modified."

[i] Draft Guidance for Industry: Survey Methodologies to Assess REMS Goals That Relate to Knowledge. 2019. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/survey-methodologies-assess-rems-goals-relate-knowledge

Because the goal of your proposed REMS is knowledge based, a survey to evaluate stakeholders' understanding of the serious risk associated with Stoboclo use will serve as an important tool to assess whether the REMS is meeting its goal.

2. Metric #6, Overall Assessment of REMS Effectiveness, was revised to align with that of the Assessment Plans of previously approved REMS for similar products.

Resubmission Instructions

Submit a REMS amendment by **COB June 7, 2024,** that addresses these comments. Include in your response an updated REMS Supporting Document including the revised REMS Assessment Plan in Word tracked changes, Word clean, and a clean PDF version.

Revised Stoboclo Assessment Plan

The revised Stoboclo REMS assessment plan must include, but is not limited to, the following (additions are noted with underline and deletions with strikethrough):

<u>For each metric, provide the two previous, current, and cumulative reporting periods (if applicable), unless otherwise noted</u>.

Program Outreach and Communication:

1. REMS Communication Plan activities: (*Provide data for 18-month report only)
    a. *Number of <u>Healthcare Providers (</u>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 hardcopy 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.

Program Implementation and Operations

2. REMS Program Implementation (*Provide data for 18-month report only)
    a. *Date of first commercial distribution of Stoboclo
    b. *Date when the Stoboclo REMS website became live and fully operational
    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. Stoboclo utilization information including but not limited to indication and type of prescribing HCPs (i.e., endocrinologist, general practitioner, internist, etc.)

Health Outcomes and/or Surrogates of Health Outcomes

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

Knowledge

5. 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 Stoboclo; 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.

(b) (4)

Overall Assessment of REMS Effectiveness (b) (4)

(b) (4)

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.

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/s/

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