Summary Review Memorandum

Date	See Electronic Stamp Date
From	Sabiha Khan, MD (Clinical Reviewer, OTBB) Michelle Luo, MD, PhD (CTL, CDTL, OTBB) Theresa Kehoe, MD (Division Signatory, DGE) Christy Osgood, MD (Division Signatory, DO1)
Subject	Request for Approval for Interchangeability after Provisional Determination - Summary Review of Amendment to BLA 761404/Original 2
Application Type	351(k) BLA
BLA/Supplement Number	761404/Original 2
Received Date	April 29, 2025
Target Action Date	October 29, 2025
Division/Office	Division of General Endocrinology (DGE) and Division of Oncology 1 (DO1)
Proprietary Name	Stoboclo (proposed interchangeable biosimilar to US-licensed Prolia (US-Prolia)); and Osenvelt (proposed interchangeable biosimilar to US-licensed Xgeva (US-Xgeva))
Proper Name	denosumab-bmwo
Product Code	CT-P41
Reference Product	US-Prolia/Xgeva (denosumab)
Pharmacologic Class	Receptor Activator of Nuclear Factor Kappa B (RANK) Ligand (RANKL) Inhibitor
Applicant	Celltrion, Inc.
Approved Indication(s)	Stoboclo (proposed interchangeable biosimilar to US-Prolia): • Treatment of postmenopausal women with osteoporosis at high risk for fracture defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures. • Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. • Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of

	prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. • Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients denosumab also reduced the incidence of vertebral fractures. • Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. Osenvelt (proposed interchangeable biosimilar to US-Xgeva): • Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors. • 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. • Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.
Purpose of the Submission	Approval of Stoboclo (denosumab-bmwo) as interchangeable with US-Prolia (denosumab) and Osenvelt (denosumab-bmwo) as interchangeable with US-Xgeva (denosumab) as follows per the provisional determination letter dated February 28, 2025: • Stoboclo (denosumab- bmwo) 60 mg/mL injection for subcutaneous use in a single-dose prefilled syringe (PFS) as interchangeable with US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS, and • Osenvelt (denosumab- bmwo) 120 mg/1.7 mL (70mg/mL) injection for subcutaneous use in a single-dose vial (vial) as interchangeable with US-Xgeva (denosumab) 120 mg/1.7 mL (70mg/mL) injection for subcutaneous use in a vial.
New Indication(s) and/or Population(s)	N/A
New Dosing Regimen(s)	N/A
Recommendation on Regulatory Action	Approval of: • Stoboclo (denosumab- bmwo) 60 mg/mL injection for subcutaneous use in a PFS as interchangeable with

	US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS, and • Osenvelt (denosumab- bmwo)120 mg/1.7 mL (70mg/mL) injection for subcutaneous use in a vial as interchangeable with US-Xgeva (denosumab) 120 mg/1.7 mL (70mg/mL) injection for subcutaneous use in a vial.

1. Background/Regulatory History

The subject of this review is the amendment submitted on April 29, 2025, to BLA 761404/Original 2 to seek approval for interchangeability of all products under the application that previously received a provisional determination on February 28, 2025.

On November 30, 2023, Celltrion, Inc. (Applicant) submitted a Biologics License Application (BLA) 761404 under section 351(k) of the Public Health Service (PHS) Act seeking licensure of Stoboclo (denosumab-bmwo) injection and Osenvelt (denosumab-bmwo) injection, product code CT-P41, as an interchangeable biosimilar product as follows:

- Stoboclo (denosumab-bmwo) injection 60 mg/mL in a single-dose prefilled syringe (PFS) for subcutaneous use as an interchangeable biosimilar with US-Prolia (denosumab) 60 mg/mL in a PFS for subcutaneous use, and
- Osenvelt (denosumab-bmwo) injection 120 mg/1.7 mL (70mg/mL) in a single-dose vial (vial) for subcutaneous use as an interchangeable biosimilar with US-Xgeva (denosumab) 120 mg/1.7 mL (70mg/mL) in a vial for subcutaneous use.

The data and information submitted in the original BLA supported licensure of Stoboclo and Osenvelt as biosimilar products. The Applicant included a scientific justification that Stoboclo and Osenvelt will produce the same clinical result in any given patient for each condition of use for which licensure is sought and for which US-Prolia and US-Xgeva have been approved, a scientific justification for extrapolating data and information to support licensure of Stoboclo and Osenvelt as interchangeable for each indication for which licensure is sought and for which US-Prolia and US-Xgeva have been previously approved, and use-related risk analyses and comparative analyses for the PFS platform. The data and information in the BLA demonstrated that Stoboclo and Osenvelt can be expected to produce the same clinical result as US-Prolia and US-Xgeva, respectively, in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between the use of Stoboclo and US-Prolia or Osenvelt and US-Xgeva is not greater than the risk of using US-Prolia or US-Xgeva without such alternation or switch.

After reviewing BLA 761404, FDA did not identify any deficiencies that would justify a complete response action. FDA considered whether any unexpired first interchangeable exclusivity precluded approval of any products in the BLA as interchangeable. Stoboclo and Osenvelt could not be approved as interchangeable at that time due to unexpired first interchangeable exclusivity for Jubbonti (denosumab-bbdz) injection 60 mg/mL for subcutaneous use and Wyost (denosumab-bbdz) injection 120 mg/1.7 mL (70 mg/mL) for subcutaneous use. Refer to the Purple Book at https://purplebooksearch.fda.gov for more information about unexpired first interchangeable exclusivity.

Therefore, BLA 761404 was administratively split to facilitate the following:

- An approval action for BLA 761404/Original 1:
    - Stoboclo (denosumab-bmwo) 60 mg/mL injection for subcutaneous use in a PFS as biosimilar to US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS, and
    - Osenvelt (denosumab-bmwo) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial as biosimilar to US-Xgeva (denosumab) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial.

- A provisional determination for BLA 761404/Original 2:
    - Stoboclo (denosumab-bmwo) 60 mg/mL injection for subcutaneous use in a PFS meets the applicable standards for interchangeability with US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS,
    - Osenvelt (denosumab-bmwo) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial meets the applicable standards for interchangeability with US-Xgeva (denosumab) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial.

The “Biosimilar Multidisciplinary Evaluation and Review” (BMER) documenting the Agency’s review of BLA 761404 dated February 27, 2025, is incorporated herein by reference.

BLA 761404/Original 1 received an approval letter dated February 28, 2025, and BLA 761404/Original 2 received a provisional determination letter dated February 28, 2025. The provisional determination letter instructed the Applicant to submit an amendment no more than six months prior to the date it believed that the application would be eligible for approval.

2. Request for Approval

To obtain approval of Stoboclo (denosumab-bmwo) 60 mg/mL injection for subcutaneous use in a PFS and Osenvelt (denosumab-bmwo) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial and in a PFS as interchangeable products, the Applicant submitted an amendment, “REQUEST FOR APPROVAL (amendment) – Licensure for Interchangeability of Stoboclo® and Osenvelt®,” under BLA 761404/Original 2 on April 29, 2025, which is the subject of this review

3. Summary Recommendations

The provisional determination letter issued February 28, 2025, states, “[i]n addition to a safety update, the amendment should also identify changes, if any, in the application, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS).”

In its Request for Approval dated April 29, 2025, the Applicant noted the submission of three prior-approval supplements (PAS) for Stoboclo and Osenvelt, which have all since been approved:

- 761404/S-001 – Change of Approved Stability Protocol and Extension of Shelf-life for Vial DP, submitted March 7, 2025
- 761404/S-002 – Addition of (b) (4) Manufacturing Site, submitted March 7, 2025
- 761404/S-003 – Addition of Unbranded Biological Product Labeling, submitted March 21, 2025

The Applicant has submitted (b) (4) additional PAS that are currently pending:

Review of Supplements (b) (4) is ongoing.

On June 26, 2025, the Applicant submitted a Periodic Adverse Experience Report (PADER) for Stoboclo and Osenvelt covering the safety reporting period from February 28, 2025, to May 27, 2025. On September 29, 2025, the Applicant submitted a PADER for Stoboclo and Osenvelt covering the safety reporting period from May 28, 2025, to August 27, 2025. The review team identified no safety concerns in their review of both PADERs.

In its Request for Approval dated April 29, 2025, the Applicant stated no changes have been made to the REMS since the approval of the original BLA. In the interim, the Stoboclo REMS was modified on September 10, 2025, to incorporate the unbranded biological product.

The review team considered the changes and updates to the application, including the ongoing review of (b) (4) supplements, and determined that they do not change our previous determination that BLA 761404/Original 2 meets the applicable standards for interchangeability.

4. Labeling

The Applicant submitted revised draft branded product and unbranded biological product labeling for Stoboclo and Osenvelt that incorporated relevant information from the updated Prolia and Xgeva labeling, respectively, with appropriate modifications. The review team determined that the proposed labeling for Stoboclo and Osenvelt is

compliant with the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

The final branded product and unbranded biological product labeling for both Stoboclo and Osenvelt will be attached to the approval letter.

5. Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, a biological product that is interchangeable with the reference product is not considered to have a "new active ingredient" for purposes of PREA.

At the time BLA 761404/Original 1 was approved on February 28, 2025, a PREA PMR was issued:

4792-1 Provide an assessment of Stoboclo (denosumab-bmwo) for the treatment of glucocorticoid-induced osteoporosis in pediatric patients 5 to 17 years of age.

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The Applicant submitted revised labeling to align with changes to the US-Prolia labeling updates approved on May 22, 2025, which updated subsection 8.4 Pediatric Use in the USPI. The updated labeling states that safety and effectiveness of Stoboclo have not been established in pediatric patients, including for patients aged 5-17 years with glucocorticoid-induced osteoporosis (GIOP). The Applicant fulfilled PREA requirements for this indication by including the relevant pediatric information in the labeling.

PeRC discussed this application on October 7, 2025, and agreed this product is assessed in pediatric patients 5 to 17 years of age for the GIOP indication and that PREA PMR 4792-1 is fulfilled.

6. REMS and Postmarketing Requirements and Commitments

6.1. Recommendations for Risk Evaluation and Mitigation Strategies

US-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. The US-Prolia REMS consists of a communication plan (CP) and timetable for submission of assessments.

Stoboclo was approved with a REMS on February 28, 2025, and last modified on September 10, 2025. The Stoboclo REMS is comparable to the US-Prolia REMS and is designed to communicate the same key risk messages and achieve the same level of safety. The requirements of the Stoboclo REMS also apply to any unbranded denosumab-bmwo distributed by the Applicant. No modifications to REMS were proposed as part of this Orig-2 submission.

The Stoboclo REMS goal and objective are:

> 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
>
> The REMS elements consist of a Communication plan (CP) and timetable for submission of assessments.

The Communication Plan materials include:

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

Timetable for submission of assessments is at 18 months, 3 years, and 7 years from the date of the initial approval of the REMS.

The currently approved REMS for Stoboclo will be attached to the approval letter.

6.2 Postmarketing Requirements and Commitments

The Applicant has fulfilled the following PMR:

4792-1 Provide an assessment of Stoboclo (denosumab-bmwo) for the treatment of glucocorticoid-induced osteoporosis in pediatric patients 5 to 17 years of age.

7. Recommended Regulatory Action

The data and information in BLA 761404/Original 2, including the information submitted by the Applicant with this amendment, are sufficient to maintain FDA's determination that Stoboclo and Osenvelt can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between use of Stoboclo and Osenvelt is not greater than the use of US-Prolia and US-Xgeva without such alternation or switch. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that:

- Stoboclo (denosumab-bmwo) 60 mg/mL injection for subcutaneous use in a PFS is interchangeable with US-Prolia 60 mg/mL injection for subcutaneous use in a PFS, and
- Osenvelt (denosumab-bmwo) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial is interchangeable with US-Xgeva 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial.

These Stoboclo and Osenvelt (denosumab- bmwo) products have met the statutory interchangeability requirements for the following indications for which US-Prolia and US-Xgeva have been previously approved:

Stoboclo:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients denosumab also reduced the incidence of vertebral fractures.
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

Osenvelt:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.
- 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.
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

As noted in the Purple Book (https://purplebooksearch.fda.gov), the applicable first interchangeable exclusivity expiration dates are:

- Jubbonti (denosumab-bbdz) 60 mg/mL injection for subcutaneous use: October 29, 2025
- Wyost (denosumab-bbdz) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use: October 29, 2025

The recommended regulatory action is approval of:

- Stoboclo (denosumab-bmwo) 60 mg/mL injection for subcutaneous use in a PFS is interchangeable with US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS, and
- Osenvelt (denosumab-bmwo) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a single-dose vial and in a PFS is interchangeable with US-Xgeva (denosumab) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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