CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761404Orig2s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Product Quality Assessment III

LABELS AND LABELING ASSESSMENT

Date of Assessment:	February 27, 2025
Assessor:	Jennifer Kim, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Qiong Fu, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XIV
Application:	BLA 761404
Applicant:	CELLTRION, Inc.
Submission Date:	November 30, 2023
Product:	Osenvelt (denosumab-bmwo) Stoboclo (denosumab-bmwo)
Dosage form(s):	Injection
Strength and Container-Closure:	120 mg/1.7 mL (70.6 mg/mL) in single-dose vial 60 mg/mL in single-dose prefilled syringe
Purpose of assessment:	The Applicant submitted a biologics license application to seek approval of Osenvelt (denosumab-bmwo) for prevention of skeletal-related events in patients with multiple myeloma in patients with bone metastases from solid tumors as an interchangeable to the reference product Xgeva (denosumab) BLA 125320 and Stovoclo (denosumab-bmwo) for reducing bone turnover, bone fractures, and osteoporosis where there are hormonal deficits, natural or therapy induced as an interchangeable biosimilar to the reference product Prolia (denosumab) BLA 125320.
Recommendations:	The prescribing information, medication guide, container labels, and carton labeling are **acceptable** from an OPQA III labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices (see Appendix B).

CONCLUSION

The prescribing information and medication guide submitted on February 26 and February 27, 2025, container labels and carton labeling submitted on February 26, 2025, were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Medication Guide (submitted on November 30, 2023)
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  \\CDSESUB1\EVSPROD\bla761404\0001\m1\us\draft-labeling-text-60mg-pfs-s.docx

- Container Labels (submitted on November 30, 2023)

(b) (4)

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

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(i), 21 CFR 600.3(k)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the proper name to read "denosumab-bmwo" for consistency with the prescribing information. *The applicant revised as requested.* For Stoboclo container label, revise the dosage form to read "Injection" for consistency. *The applicant revised as requested.*	

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(i)(1), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Comment/Recommendation: *The Stoboclo container label is small and could be considered a partial label. Thus, the qualifying phrase "Manufactured by", manufacturer address, and U.S. license number are not required per 21 CFR 610.60(c).*

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(i)(1)	✓ Yes ☐ No ☐ N/A

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: For Osenvelt container label, revise the product strength to express as total quantity per total volume followed by the concentration per mL in accordance with USP General Chapter <7> as follows: "120 mg/1.7 mL (70 mg/mL)". *The applicant revised as requested.*	

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *The Stoboclo container label is small and would be considered a partial label. Thus, a Medication Guide statement is not required per 21 CFR 610.60(c).*	

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The container is enclosed in a package.*	

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The product contains a container label.*	

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. *The applicant confirms that there is no text on the ferrule and cap overseal of the vials.*	

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No

	☐ N/A
Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located. *The applicant confirms that sufficient area of the container remains uncovered for its full length to allow for visual inspection. Also, the label is made of transparent material, there are no obstacles to visual inspection.*	

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *The Stoboclo container label is small and could be considered a partial label. Thus, a route of administration is not required.* For Stoboclo container label, revise the route of administration statement to read "For subcutaneous use only" for consistency. *The applicant revised as requested.*	

***NDC numbers* (container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	☐ Yes ☐ No ☒ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: *The Stoboclo container label is small and could be considered a partial label. Thus, a package type term is not required per 21 CFR 610.60(c).*

No misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	✓ Yes ☐ No ☐ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The label does not display text in Spanish.*	

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The drug product does not contain FD&C Yellow No. 5 or 6.*	

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *The label is small and could be considered a partial label. Thus, a net quantity is not required per 21 CFR 610.60(c).*	

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *The Stoboclo container label is small and could be considered a partial label. Thus, a dosage statement is not required per 21 CFR 610.60(c).* For Osenvelt container label, revise the statement of dosage to read "Recommended dosage: See prescribing information." for consistency. *The applicant revised as requested.*	

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100, FD&C Act section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required per 21 CFR 610.60(c).*	

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *The Stoboclo container label is small and could be considered a partial label. Thus, an storage requirement statement is not required per 21 CFR 610.60(c).*	

Dispensing container (container label)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package[6] Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the proper name to read "denosumab-bmwo" for consistency with the prescribing information. *The applicant revised as requested.*	

Manufacturer name, address, and license number (package labeling)	Acceptable
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Lot number or other lot identification (package labeling)	Acceptable
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Expiration date (package labeling)	Acceptable
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: For Osenvelt carton labeling, revise the product strength to express as total quantity per total volume followed by the concentration per mL in accordance with USP General Chapter <7> as follows: "120 mg/1.7 mL (70 mg/mL)". *The applicant revised as requested.*	

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes

	☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The drug product is not made with latex (natural rubber latex, dry natural rubber or synthetic derivatives of natural rubber latex).*	

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, acetic acid, sodium acetate, sorbitol, and polysorbate 20. Confirm if sodium acetate (b) (4) meets the definition of the sodium acetate, USP monograph. If so, then the name and the calculated amount (calculated on the dried basis not the (b) (4) basis) will need to be revised accordingly. Confirm the provided calculation and provide an updated Description and Composition Table in section 3.2.P.1 adding a footnote to Table 1 that includes the calculation between mg of sodium acetate (b) (4) and mg of sodium acetate (b) (4) (labeled as sodium acetate). The footnote	

should serve as a link between the name and quantity presented in section 3.2.P.1 (i.e., sodium acetate [redacted] (b) (4) to the name and quantity presented in the Prescribing Information, container label, and carton labeling (i.e., sodium acetate).

Revise the content statement by using the established names and include the net quantity as total volume as follows:

Each 1.7 mL of solution contains:

Denosumab-bmwo	120 mg
Acetic acid	0.44 mg
Polysorbate 20	0.17 mg
Sodium acetate	1.78 mg
Sorbitol	79.9 mg
Water for Injection	

Revise the content statement by using the established names and include the net quantity as total volume as follows:

Each 1 mL of solution contains:

Denosumab-bmwo	60 mg
Acetic acid	0.26 mg
Polysorbate 20	0.1 mg
Sodium acetate	1.05 mg
Sorbitol	47 mg
Water for Injection	

The applicant revised as requested.

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OPQA III Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for denosumab products (i.e., there is no specific test method described in regulation for denosumab products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for Osenvelt and Stoboclo because lot variability is not a concern as the manufacturing process is*	

appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	✓ Yes ☐ No ☐ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No

	☐ N/A

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

No misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	✓ Yes ☐ No ☐ N/A

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The label does not display text in Spanish.*	

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The drug product does not contain FD&C Yellow No. 5 or 6.*	

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The drug product does not contain phenylalanine.*	

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The drug product does not contain sulfites.*	

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *See comments for inactive ingredients.*	

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: For Osenvelt carton labeling, revise Statement of Dosage to read "Recommended Dosage: See prescribing information." for consistency. *The applicant revised as requested.*	

Dispensing container (package labeling)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A

Other (package labeling)	Acceptable
	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the statement on the principal display panel (PDP) from "(b) (4) " to read "Stoboclo 60 mg/mL is administered once every 6 months" to consistent presentation of product strength. *The applicant revised as requested.* Revise the statement on the PDP from "(b) (4) " to read "See Prescribing Information for Full Prescribing and Manufacturing Information." *The applicant revised as requested.* Revise the statement "(b) (4)" to read "Each carton contains one Single-dose Prefilled Syringe with safety guard" and relocate it away from and less prominent than the product strength, such as to the bottom of the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022). *The applicant revised as requested.*	

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: For Stoboclo, we revised to a format that is consistent with other product labeling. *The applicant revised as requested.*	

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv) *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components *Draft Guidance Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry* (January 2023)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised to the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit." per 21 CFR 201.57(c)(3)(iv). *The applicant revised as requested.*	

We deleted "(b) (4)" because the drug product does not contain any particles. *The applicant revised as requested.*

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We added the description of the drug product. *The applicant revised as requested.*	

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q), FD&C Act Section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: For Osenvelt labeling, we revised the description of the drug substance to be consistent with the Stoboclo labeling. *This comment was not communicated to the applicant, because the review team preferred to keep the description language consistent with the reference product labeling.* We deleted the proprietary name from the first paragraph, which describes the drug substance. *The applicant revised as requested.* We added the proper name and dosage form to the second paragraph describing the drug product. *The applicant revised as requested.* We added the route of administration. *The applicant revised as requested.*	

We revised the inactive ingredient names to appear in alphabetical order and revised the quantity in mg.
The applicant revised as requested.

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, acetic acid, sodium acetate, sorbitol, and polysorbate 20. Confirm if sodium acetate (b) (4) meets the definition of the sodium acetate, USP monograph. If so, then the name and the calculated amount (calculated on the (b) (4) not the (b) (4) basis) will need to be revised accordingly. Confirm the provided calculation and provide an updated Description and Composition Table in section 3.2.P.1 adding a footnote to Table 1 that includes the calculation between mg of sodium acetate (b) (4) and mg of sodium acetate (b) (4) (labeled as sodium acetate). The footnote should serve as a link between the name and quantity presented in section 3.2.P.1 (i.e., sodium acetate (b) (4) to the name and quantity presented in the Prescribing Information, container label, and carton labeling (i.e., sodium acetate).
The applicant revised as requested.

Revised labeling submitted August 14, 2024: The applicant revised the molecular weight form "147 kDa" to "(b) (4)".
Agency comment: We revised the molecular weight back to "147 kDa" for consistency with the reference product.
The applicant revised as requested.

Revised labeling submitted February 14, 2025: The applicant added "(b) (4) " in section 11 of Stoboclo prescribing information without an rationale. The agency rejected the statement because the statement is not necessary to inform safe and effective use, and it is not a required statement.
The applicant revised as requested.

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We added the appropriate dosage form. *The applicant revised as requested.* For Osenvelt labeling, we added the product strength in mg/mL within the parenthesis. *The applicant revised as requested.* We revised the language for consistency with other product labeling and clarity. *The applicant revised as requested.*	

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
STORAGE AND HANDLING	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised the active ingredient names to its established names to fulfil the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e). *The applicant revised as requested.*	

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Add manufacturer information. *The applicant revised as requested.*	

Patient Information Labeling Evaluation: N/A

Instructions for Use Evaluation: N/A

APPENDIX C. Acceptable Labels and Labeling

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

- Prescribing Information and Medication Guide (submitted on February 26 and February 27, 2025)
  \\CDSESUB1\EVSPROD\bla761404\0037\m1\us\final-labeling-text-120mg-vial.docx

  \\CDSESUB1\EVSPROD\bla761404\0038\m1\us\final-labeling-text-60mg-pfs-s.docx

- Container Labels (submitted on February 26, 2025)

(b) (4)

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

Jennifer Kim

Digitally signed by Jennifer Kim
Date: 2/27/2025 08:36:26AM
GUID: 5e5438d2008138bdbae1db8d4abc0580

Qiong Fu

Digitally signed by Qiong Fu
Date: 2/27/2025 08:48:22AM
GUID: 5c5af23f004dca70cf7a20351e44cac2

BLA Executive Summary Addendum
Assessment Date: February 18, 2025

Addendum: This addendum has been prepared to document the final OPQ recommendation on approvability of BLA 761404 following the determination of compliance status for the manufacturing facilities for this BLA and finalization of the microbiology assessment. For additional summary information on the comparative analytical assessment, refer to the OPQ IQA executive summary memorandum uploaded to Panorama and DARRTS on August 14, 2024.

1. Application/Product Information

BLA number	761404
Submission Type	Original Submission
Regulatory Pathway	Biosimilar 351 (k), also proposing interchangeability
Associated IND/BLA	IND 147751
Review Designation	standard review
Applicant	Celltrion Inc.
Indication	All indications currently approved for US-licensed Prolia and Xgeva, including: • 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.

	• 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
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Stoboclo (pre-filled syringe) and Osenvelt (vial) (proposed)
	Non-proprietary Name/Code Name denosumab-bmwo/ CT-P41 (company code)
	OBP Naming: MAB HUMAN (IGG2) ANTI O14788 (TNF11_HUMAN) [CTP41]
Drug Product Description	Sterile, preservative-free, colorless to to pale yellow solution supplied in a single-dose vial or pre-filled syringe (PFS) assembled with a needle safety device. Each single dose vial contains 120 mg denosumab-bmwo, (b) (4) acetate, 4.7% sorbitol, 0.01% polysorbate 20 at pH 5.2 and Water for Injection (USP). Each single dose PFS contains 60 mg denosumab-bmwo (60 mg/mL solution), (b) (4) acetate, 4.7% sorbitol, 0.01% polysorbate 20 to a pH of 5.2 and Water for Injection (USP). Denosumab-bmwo is a therapeutic recombinant human IgG2 monoclonal antibody with affinity and specificity for human RANKL (receptor activator of nuclear factor kappa-B ligand). Denosumab-bmwo has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

Dosage Form	Solution for injection		
Strength	60 mg/pre-filled syringe (60 mg/1 mL) 120 mg/vial (120 mg/1.7 mL)		
Route of Administration	Subcutaneous		
Primary Container Closure System	60 mg/1 mL PFS: 1 mL (b) (4) glass syringe with a staked-in-place stainless steel needle and closed with a (b) (4) elastomeric plunger-stopper and an elastomeric needle shield (cap). 120 mg/1.7 mL vial: 3mL (b) (4) glass vial closed with a 13 mm elastomeric stopper and flip-off seal		
Device Information	The PFS has a 27-gauge fixed ½ inch staked-in-place stainless steel needle and is assembled with a finger flange, plunger rod and fitted with a passive safety guard.		
Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Qiong Fu	Yetao Jin
	Drug product	Qiong Fu	Yetao Jin
	Immunogenicity Assay	Qiong Fu	Yetao Jin
	Facility	Hamet Toure (drug substance (DS)) Maria Gutierrez-Hoffman (drug product (DP))	Virginia Carroll
	Microbiology	Hamet Toure (DS)	Virginia Carroll

		Maria Gutierrez-Hoffman (DP)	
	RBPM	Kelly Ballard	
	ATL	Yetao Jin	
OPQ Issued Consults	CDRH/ODE and OC		

2. Recommendation and Conclusion on Approvability
Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761404 for Stoboclo and Osenvelt manufactured by Celltrion Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Stoboclo and Osenvelt is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Stoboclo and Osenvelt is highly similar to US-licensed Prolia and Xgeva, notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:** CELLTRION, Inc., Plant II (CLT2), 20, Academy-ro-51 beon-gil, Yeonsu-gu, Incheon, 22014, Republic of Korea (FEI: 3005241015).
- **Drug Product:**
  - Single dose vial: (b) (4)
  - PFS: (b) (4) CELLTRION Pharm, Inc. (CLT-Pharm), 82, 2 Sandan-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, 28117, Republic of Korea (FEI: 3012279978) (Assembly and secondary packaging (labeling and cartonning) of CT-P41 drug product (PFS-S)).

b. Fill size and dosage form:

- Single dose vial: supplied as a 120 mg/1.7 mL solution in a single dose vial.

- PFS: supplied as a 60 mg/mL solution in a single dose prefilled syringe assembled with a needle safety device.

c. Dating Period:
- Drug Product:
- Single dose vial: 36 months at 5°C ± 3°C. It can be stored at room temperature up to a maximum of 25 ℃ (77 ℉) for a period of up to 30 days in the carton to protect from light and should not be refrigerated afterward.
- PFS: 48 months at 5°C ± 3°C. It can be stored at room temperature up to a maximum of 25 ℃ (77 ℉) for a period of up to 30 days and should not be refrigerated afterward.
- Drug Substance:

(b) (4)

- Intermediate Substance, if applicable: N/A
- For copackaged products: Not copackaged
- Stability Option:
  - For stability protocols:
    - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and/or drug product under 21 CFR 601.12.

d. Exempt from lot release:
- Yes
- Rationale, if exempted: Stoboclo and Osenvelt are exempted from lot release per FR 95-29960.

4. Basis for Recommendation

a. Summary:

CT-P41 is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL (receptor activator of the nuclear factor kappa-B ligand), a transmembrane or soluble protein essential for the formation, function, and survival of osteoclast, the cells responsible for bone resorption thereby modulating calcium release from bone. It is a proposed interchangeable biosimilar to US-licensed Prolia and US-licensed Xgeva for the same indications as US-licensed Prolia and US-licensed Xgeva. Potency of CT-P41 is controlled using a cell-based osteoclastogenesis inhibition assay in DS and DP release and stability testing. The primary mechanism of action (MoA) of CT-P41 is not mediated via the Fc region or activities associated with afucosylated glycans and CT-P41 was specifically developed as an IgG2 to neutralize RANKL without inducing complement activation and ADCC.

The totality of the evidence from the comparative analytical assessment supports that CT-P41 is highly similar to US-licensed Prolia and US-licensed Xgeva, notwithstanding minor differences in clinically inactive components. The strengths of CT-P41 60 mg/mL in the single-dose PFS for subcutaneous injection and 120mg/1.7mL (70mg/mL) in a single-dose vial for subcutaneous injection are the same as those of US-licensed Prolia and US-licensed Xgeva in the same presentations and routes of administration, respectively. Refer to Appendix in the OPQ IQA executive summary memorandum uploaded to Panorama and DARRTS on August 14, 2024 for detailed summary of the comparative analytical assessment.

The CT-P41 DS manufacturing process consists of (b) (4)

The DP manufacturing process for the 120 mg/1.7 mL vial presentation includes (b) (4)

The DP manufacturing process for the 60 mg/1 mL PFS presentation includes (b) (4)

The OPMA's final determination of compliance status of the manufacturing facilities has concluded with "approve" recommendations for the DS manufacturing facility Celltrion, Inc, Plant II, Incheon, Republic of Korea (FEI 3005241015), the DP manufacturing facilities (b) (4) and (b) (4) and the device assembly facility 82, 2 Sandan-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, 28117, Republic of Korea (FEI: 3012279978).

The OPMA's final recommendation from a product quality microbiology and

sterility perspective is also approval with the post-marketing commitments listed in section 4e of this addendum.

The Center for Devices and Radiological Health (CDRH) final recommendation is that the needle safety device of the PFS combination product is approvable.

The overall denosumab-bmwo/ Stoboclo and Osenvelt control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for denosumab-bmwo/ Stoboclo and Osenvelt are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The BLA is recommended for approval from product quality, facility, microbiology, and sterility assurance perspectives. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose.

Therefore, from an OPQ perspective, this BLA is recommended for approval.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Immunogenicity Assay	-	Adequate
Facilities	-	Adequate
Microbiology	-	Adequate with PMCs/PMRs

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

As an initial matter, we determined that no U.S. standard of potency has been prescribed for denosumab (*i.e.*, there is no specific test method described in regulation for denosumab that establishes an official standard of potency). We next considered whether potency is a factor for denosumab within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for Stoboclo and Osenvelt for purposes of § 610.61(r) because lot variability is not a concern for Stoboclo and Osenvelt as Stoboclo and

Osenvelt's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps

- To conduct an additional endotoxin method verification with the [(b) (4)] samples and assess the sample [(b) (4)] This will ensure that the method is suitable for the detection of endotoxin per USP <85>. Three batches from the [(b) (4)] samples will be used.
- To repeat the plunger movement study of the CT-P41 pre-filled syringe to ensure that sterility of the drug product is not impacted under worst case transportation conditions. This additional study will be performed using syringes with the worst-case plunger insertion depth (largest air bubble) considering the actual shipping condition of CT-P41.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:

[(b) (4)]

ii. Residual risk: N/A

iii. Future inspection points to consider: N/A

c. Drug Product:

i. Protocols approved:

- Container closure system (CCS) leachable study protocol for PFS DP under long-term conditions
- Primary PFS DP stability study protocol (long-term)
- Post-approval annual stability study protocol for PFS DP
- CCS leachable study protocol for vial DP under long-term conditions
- Primary vial DP stability study protocol (long-term)
- Post-approval annual stability study protocol for vial DP
- Shipping validation protocol for change in shipping conditions (for transportation of CT-P41 DS, PFS DP or vial DP)

ii. Residual risk: N/A

iii. Future inspection points to consider: N/A

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Appendix. Comparative Analytical Assessment Summary
(Refer to the OPQ IQA executive summary memorandum uploaded to Panorama and DARRTS on August 14, 2024.)

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/

YETAO JIN
02/18/2025 04:00:00 PM

BLA Executive Summary
Assessment Date: Assessment Date: August 14, 2024

1. Application/Product Information

BLA number	761404
Submission Type	Original Submission
Regulatory Pathway	Biosimilar 351 (k), also proposing interchangeability
Associated IND/BLA	IND 147751
Review Designation	standard review
Applicant	Celltrion Inc.
Indication	All indications currently approved for US-licensed Prolia and Xgeva, including: • 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. • 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

Rx/OTC dispensed	Rx
Drug Product Name	**Proprietary Name:** Stoboclo (pre-filled syringe) and Osenvelt (vial) (proposed)
	Non-proprietary Name/Code Name denosumab-bmwo/ CT-P41 (company code)
	OBP Naming: MAB HUMAN (IGG2) ANTI O14788 (TNF11_HUMAN) [CTP41]
Drug Product Description	Sterile, preservative-free, colorless to to pale yellow solution supplied in a single-dose vial or pre-filled syringe (PFS) assembled with a needle safety device. Each single dose vial contains 120 mg denosumab-bmwo, (b) (4) acetate, 4.7% sorbitol, 0.01% polysorbate 20 at pH 5.2 and Water for Injection (USP). Each single dose PFS contains 60 mg denosumab-bmwo (60 mg/mL solution), (b) (4) acetate, 4.7% sorbitol, 0.01% polysorbate 20 to a pH of 5.2 and Water for Injection (USP). Denosumab-bmwo is a therapeutic recombinant human IgG2 monoclonal antibody with affinity and specificity for human RANKL (receptor activator of nuclear factor kappa-B ligand). Denosumab-bmwo has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.
Dosage Form	Solution for injection
Strength	60 mg/pre-filled syringe (60 mg/1 mL) 120 mg/vial (120 mg/1.7 mL)
Route of Administration	Subcutaneous
Primary Container Closure System	**60 mg/1 mL PFS:** 1 mL (b) (4) glass syringe with a staked-in-place stainless steel needle and closed with a (b) (4) elastomeric plunger-stopper and an elastomeric needle shield (cap).

	120 mg/1.7 mL vial: 3mL (b) (4) glass vial closed with a 13 mm elastomeric stopper and flip-off seal		
Device Information	The PFS has a 27-gauge fixed ½ inch staked-in-place stainless steel needle and is assembled with a finger flange, plunger rod and fitted with a passive safety guard.		
Co-packaged Product Information	N/A		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance	Qiong Fu	Yetao Jin
	Drug product	Qiong Fu	Yetao Jin
	Immunogenicity Assay	Qiong Fu	Yetao Jin
	Facility	Hamet Toure (DS) Maria Gutierrez-Hoffman (DP**)**	Virginia Carroll
	Microbiology	Hamet Toure (DS) Maria Gutierrez-Hoffman (DP**)**	Virginia Carroll
	RBPM	Kelly Ballard	
	ATL	Yetao Jin	
OPQ Issued Consults	CDRH/ODE and OC		

2. Recommendation and Conclusion on Approvability

Recommendation: Pending

The Office of Pharmaceutical Quality (OPQ), CDER, recommendation on approvability of BLA 761404 for Stoboclo and Osenvelt manufactured by Celltrion Inc is pending the final determination of compliance status of the manufacturing facilities and the completion of the microbiological assessment.

3. Basis for Recommendation

a. Summary:

CT-P41 is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL (receptor activator of the nuclear factor kappa-B ligand), a transmembrane or soluble protein essential for the formation, function, and survival of osteoclast, the cells responsible for bone resorption thereby modulating calcium release from bone. It is a proposed interchangeable biosimilar to US-licensed Prolia and US-licensed Xgeva for the same indications as US-licensed Prolia and US-licensed Xgeva. Potency of CT-P41 is controlled using a cell-based osteoclastogenesis inhibition assay in drug substance (DS) and drug product (DP) release and stability testing. The primary mechanism of action (MoA) of CT-P41 is not mediated via the Fc region or activities associated with afucosylated glycans and CT-P41 was specifically developed as an IgG2 to neutralize RANKL without inducing complement activation and ADCC.

The totality of the evidence from the comparative analytical assessment supports that CT-P41 is highly similar to US-licensed Prolia and US-licensed Xgeva, notwithstanding minor differences in clinically inactive components. The strengths of CT-P41 60 mg/mL in the single-dose PFS for subcutaneous injection and 120mg/1.7mL (70mg/mL) in a single-dose vial for subcutaneous injection are the same as those of US-licensed Prolia and US-licensed Xgeva in the same presentations and routes of administration, respectively. Refer to Appendix for detailed summary of the comparative analytical assessment.

The CT-P41 DS manufacturing process consists of (b) (4)

The DP manufacturing process for the 120 mg/1.7 mL vial presentation includes (b) (4)

The DP manufacturing process for the 60 mg/1 mL PFS presentation includes (b) (4)

(b) (4)

The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose.

The recommendation from the Center for Devices and Radiological Health (CDRH) is for approval of the device component of the application. CDRH defers to the Office of Pharmaceutical Manufacturing Assessment (OPMA) for the assessment of the device assembly and secondary packaging site at 82, 2 Sandan-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, 28117, Republic of Korea (FEI: 3012279978).

The final recommendation from the OPQ is pending the determination of facilities and the completion of the microbiological assessment from the OPMA.

b. Subdiscipline Recommendation:

At this time the final recommendation from OPQ is pending. The subdiscipline recommendations will be updated in a future addendum to this memorandum upon determination of the manufacturing facility compliance and completion of the microbiology assessment by the OPMA.

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Immunogenicity Assay	**-**	**Adequate**
Facilities	**-**	**Pending**
Microbiology	**-**	**Pending**

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

Not applicable as OPQ does not recommend approval of this application.

4. Life-Cycle Considerations

Not applicable as OPQ does not recommend approval of this application.

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Appendix. Comparative Analytical Assessment Summary

A. Overview and Conclusions

Celltrion is seeking licensure of CT-P41 as an interchangeable biosimilar to US-licensed Prolia and US-licensed Xgeva for the following strengths and presentations: 60 mg/1.0 mL (60 mg/mL) in a single-dose prefilled syringe (PFS) with safety guard for subcutaneous injection, and 120 mg/1.7 mL (70 mg/mL) in a single-dose vial for subcutaneous injection. These are corresponding to the same strengths and presentations as currently available for US-licensed Prolia and US-licensed Xgeva, respectively. The 60 mg/1.0 mL PFS presentation has the same qualitative and quantitative formulation as US-licensed Prolia. The formulation of the 120 mg/1.7 mL vial presentation is qualitatively the same as US-licensed Xgeva but differs slightly qualitatively, with respect to the content of sodium acetate and sorbitol (CT-P41 Vial drug product (DP) contains (b) (4) sodium acetate and 4.7% sorbitol (w/v) while US-licensed Xgeva contains (b) (4) sodium acetate and 4.6% sorbitol (w/v)). These minor differences are not anticipated to impact product quality, safety, or potency.

To support a demonstration that CT-P41 PFS drug product (DP) is highly similar to US-licensed Prolia, Celltrion performed an extensive comparative analytical assessment (CAA) with the following materials:

- 10 lots of US-licensed Prolia with expiration dates ranging from April 2023 through March 2025;
- 6 lots of CT-P41 PFS DP manufactured between January 2021 and March 2023 from 6 independent CT-P41 drug substance (DS) lots.
- For the assays not expected to be impacted by the DP manufacturing process, independent CT-P41 DS lots were included in the CAA if a DP lot manufactured from that DS lot was not available. Additional 4 DS lots manufactured between October 2022 and November 2022 independent of the 6 lots of CT-P41 PFS DP mentioned above were used in this CAA for a total of 10 lots including the 6 CT-P41 PFS DP lots.

In addition, per the meeting discussions with the Agency during development, and consistent with our current approach of leveraging CAA from one strength and presentation to support the assessment of an additional strength and presentation, Celltrion performed a targeted CAA with reduced numbers of CT-P41 vial DP and US-licensed Xgeva lots for quality attributes (QAs) except protein concentration of the vial presentation using the following materials:

- 3 lots of US-licensed Xgeva with expiration dates ranging from December 2023

through October 2024. For assessment of protein concentration only, additional 7 lots of US-licensed Xgeva were used for a total of 10 lots.

- 3 lots of CT-P41 vial DP manufactured in July 2023 from 3 independent CT-P41 DS lots. For assessment of protein concentration only, additional 4 independent CT-P41 DS lots were used that were assessed as supporting information to the DP lot data.

The DP lots used in clinical studies and the CT-P41 PPQ lots for both presentations were included in the CAA. The ages of US-licensed Prolia and US-licensed Xgeva at the time of testing were adequate to capture potential differences or variability over time.

The CAA included comparison of physicochemical and functional QAs of CT-P41 PFS and vial DP to US-licensed Prolia and US-licensed Xgeva, respectively, using qualified orthogonal state-of-art methods, as well as comparison of their degradation profiles under forced degradation conditions. Some QAs, such as host cell proteins (HCP), host cell DNA (HCD), are not appropriate for direct comparison of CT-P41 to US-licensed Prolia/US-licensed Xgeva due to differences in the manufacturing processes and different production host cells. These attributes, together with QAs as visual appearance, pH, osmolarity, particulate matter (visible and subvisible particulate), and extractable volume were not included in the comparative analytical studies but assessed as part of the commercial manufacturing process controls of CT-P41. This approach is consistent with recommendations in the FDA draft guidance for industry *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019).

The CAA included an extensive comparative assessment between the CT-P41 PFS DP and US-licensed Prolia since this presentation was used in the clinical studies and a targeted comparative assessment using the same methods, with reduced lot numbers for QAs except protein concentration, for CT-P41 vial DP and US-licensed Xgeva. The Applicant used a criticality-based data analysis approach to evaluate the analytical results. That was consistent with FDA recommendations. A criticality ranking of QAs is according to the risk of potential impact on activity, PK/PD, efficacy, safety, and immunogenicity. The data evaluation methods are classified into the following three categories:

- QR2: QAs with very high criticality amenable to statistical analysis were compared to quality ranges (QRs) of mean ± 2 standard deviations (SD) established from US-licensed Prolia.
- QR3: QAs with high and moderate criticality amenable to statistical analysis were compared to QRs of mean ± 3 SD established from US-licensed Prolia or US-licensed Xgeva (for protein concentration of the vial presentation only as the values of this QA are different in the PFS and vial presentations).
- RD: Also known as Presentation of Raw/Graphical Data. This approach was used for the evaluation of results for low and very low criticality ranking QAs, data from qualitative test methods, data from orthogonal tests of QAs that have also

been analyzed using the QR approach, additional mechanism of action studies, and the comparative analytical study of CT-P41 vial DP and US-licensed Xgeva other than protein concentration.

For the comparative stability studies, the Applicant conducted studies under forced degradation conditions (high temperature, oxidation, UV light, low pH, and high pH). The comparative forced degradation studies show similar degradation pathways and degradation rates among CT-P41 DP, US-licensed Prolia, and US-licensed Xgeva.

Our assessment of the CT-P41 and US-licensed Prolia and US-licensed Xgeva comparative analytical data supports the determination that CT-P41 is highly similar to US-licensed Prolia and US-licensed Xgeva, notwithstanding minor differences in clinically inactive components. CT-P41 DP has the same strength, dosage form and route of administration as US-licensed Prolia and US-licensed Xgeva. The Applicant used a comprehensive set of analytical methods that were suitable to evaluate the critical quality attributes of CT-P41 and US-licensed Prolia/ US-licensed Xgeva to support the demonstration that the products are highly similar. The number of lots tested and data analysis approaches used were appropriate or justified as needed to allow for a meaningful evaluation of the results of the analytical studies. The differences observed in a subset of the quality attributes do not preclude a determination that CT-P41 and US-licensed Prolia/ US-licensed Xgeva are highly similar.

B. Comparative Analytical Results

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?
Primary Structure	Amino acid sequence	Yes
	Molecular Weight	Yes
Cysteine Variants	Free thiols	Yes
	Disulfide bonds	Yes
	Disulfide isoforms/ IgG2 isoforms	Yes
Higher Order Structure	Secondary structure	Yes
	Tertiary structure	Yes
	Thermal stability	Yes
Oligosaccharide Profile and N-linked glycan	Fucosylated group	Yes
	Afucosylated group	Yes
	High Mannose	Yes
	Mole Galactose/Mole denosumab	Yes
	G1F+NANA	Yes
Charge Variants	Acidic Variants	Yes
	Basic Variants	Yes

	Main Variant	Yes
	pI	Yes
	Deamidation	Yes
	N-terminal pyroglutamate	Yes
	C-terminal lysine	Yes
	C-terminal proline amide	Yes
	Glycation	Yes
Oxidation Variants	Methionine oxidation	Yes
Size Variants	Monomer	Yes
	High Molecular Weight Species	Yes
	Low Molecular Weight Species	Yes
	Intact IgG (H2L2)	Yes
	HC+LC	Yes
	Non-glycosylated heavy chain (NGHC)	Yes
Fc-mediated activity	C1q binding	Yes
	FcγRIIIa (V-type) binding	Yes
	FcγRIIIa (F-type) binding	Yes
	FcγRIIa binding	Yes
	FcγRIIb binding	Yes
	FcRn binding	Yes
Biological Activity	RANKL target binding	Yes
	RANKL binding inhibition with RANK	Yes
	RANKL binding inhibition with OPG	Yes
	Osteoclastogenesis inhibition	Yes
	Cell-based RANKL binding	Yes
Drug Product Attributes	Protein concentration	Yes

Comparative assessment of the forced degradation stability studies was performed to characterize and compare the degradation pathways of CT-P41 PFS DP versus US-licensed Prolia and CT-P41 vial DP versus US-licensed Xgeva under diverse forced degradation conditions. The products were subject to high temperature stress, oxidative stress, UV light stress, low pH, and high pH stress conditions. Considering the data and justifications for the minor differences observed, the results do not preclude a demonstration that CT-P41 DP is highly similar to US-licensed Prolia and US-licensed Xgeva.

C. Analytical Studies to Support the Use of a Non-US-Licensed Comparator Product

Not applicable.

D. Assessment of Comparative Analytical Study Results

Comparative analytical assessment criteria were met for all attributes with the following exceptions:

Critical Quality Attributes with Differences	Related Critical Quality Attributes
Size variants	Slightly higher values of monomer by SEC-HPLC were observed in CT-P41 lots (99.44- 99.70%, mean: 99.55%, 3 of 10 lots out of QR) compared to US-licensed Prolia (99.40-99.53%, mean: 99.47%, QR: 99.340-99.600%), coupled with slightly lower values of HMWS that were observed in CT-P41 lots (0.30-0.56%, mean: 0.45%, 3 of 10 lots out of QR) compared to US-licensed Prolia (0.47-0.60%, mean: 0.53%, QR: 0.400-0.660%). Similar differences were also observed between CT-P41 vial DP and US-licensed Xgeva lots. This difference is very marginal and did not impact the biological activities of the product. In addition, higher values of non-glycosylated heavy chain (NGHC) by CE-SDS (reduced) were observed in CT-P41 lots (1.48-2.77%, mean: 2.10%, 10 of 10 lots out of QR) compared to US-licensed Prolia/ (1.01-1.27%, mean: 1.14%, QR: 0.882-1.392%), coupled with slightly lower values of Purity (HC+LC) that were observed in CT-P41 lots (96.85-98.16%, mean: 97.49%, 6 of 10 lots out of QR) compared to US-licensed Prolia (97.75-98.45%, mean: 98.12%, QR: 97.560-98.676%). Similar differences were also observed between CT-P41 vial DP and US-licensed Xgeva lots. The lower levels of HC+LC in CT-P41 is due to higher levels NGHC, but NGHC does not impact biological activities except FcγRIIIa-V binding affinity. However, ADCC activity is observed for neither CT-P41 nor US-licensed Prolia. Overall, the observed differences in size variant results by different analytical methods are minor and do not preclude the demonstration that CT-P41 is highly similar to US-licensed Prolia and US-licensed Xgeva.
Charge variants	Lower values for acidic peaks (3.76-4.11%, mean: 3.89%, 10 of 10 lots out of QR) and higher values for basic peaks (12.42-23.85%, mean: 16.82%, 10 of 10 lots out of QR) and associated broader range of main peak (72.21-83.72%, mean: 79.29%, 4 of 10 lots out of QR) by IEC-HPLC were observed in CT-P41 compared to US-licensed Prolia (6.98-7.96%/mean: 7.48%/QR: 6.369-8.599%, 10.76-11.65%/mean: 11.09%/ QR: 10.352-11.822%, and 80.50-82.17%/ mean: 81.43%/QR: 80.008-82.856%, respectively). Similar differences were also observed between CT-P41 vial DP and US-licensed Xgeva lots. Differences in quality attributes that contribute to the differences observed in acidic variants include deamidation, glycation, and fragments; and in basic variants include amidation, aggregates, and fragments. Extended characterization studies on IEC-HPLC peak indicate both acidic and basic peaks are product-related substances and have comparable biological activities to each other and to the main peak. LC-MS peptide mapping results indicate

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	higher level of basic peaks is due to C-terminal proline amidation. In addition, a basic peak (Peak 6) was detected by cIEF at pI of 9.03 but not detected in US-licensed Prolia/US-licensed Xgeva. Further characterization suggested Peak 6 is also due to higher C-terminal proline amidation. Overall, CAA and extended characterization studies support that the observed differences in charge variant results by different analytical methods do not preclude the demonstration that CT-P41 is highly similar to US-licensed Prolia and US-licensed Xgeva.
Oligosaccharide profile	Higher levels of fucosylated group (87.45-88.53%, mean: 87.96%, 10 of 10 lots out of QR) and lower levels of high mannose (3.31-3.76% ,mean: 3.48%, 10 of 10 lots out of QR) were observed in CT-P41 compared to the levels detected in US-licensed Prolia (80.58-83.33%/mean: 81.78%/QR: 79.119-84.431% and 7.12-8.77%/mean: 8.07%/QR: 6.566-9.576, respectively). Similar differences were also observed between CT-P41 vial DP and US-licensed Xgeva lots. The results from further characterization of N-linked glycan suggested that Man5 levels were lower in CT-P41 (1.8-2.4% mean: 2.1%) compared to the levels in US-licensed Prolia (6.6-8.7%, mean: 7.7%). In addition, slightly lower levels of G1 in afucosylated N-glycans were observed in CT-P41 (0.3-0.4%, mean: 0.3%) compared to US-licensed Prolia (0.4-1.4%, mean: 0.8%). Similar differences were also observed between CT-P41 vial DP and US-licensed Xgeva lots. As Fc-mediated effector function is not part of denosumab MOA, differences in these N-glycan species are not expected to impact biologic activity. The magnitude of differences is unlikely to impact immunogenicity and PK, as verified by FcRn binding results as part of the CAA. Overall, the observed differences in Oligosaccharide profile and N-glycosylation results do not preclude the demonstration that CT-P41 is highly similar to US-licensed Prolia/US-licensed Xgeva.
Free thiol	Slightly higher values were observed in CT-P41 (0.59-0.63/mean: 0.61 mol SH/mol IgG) compared to US-licensed Prolia (0.44-0.49/mean: 0.47 mol SH/mol IgG). Similar differences were also observed between CT-P41 vial DP and US-licensed Xgeva lots. This difference is minor and is not anticipated to impact safety, efficacy, or immunogenicity. Overall, the observed differences in free cystines results do not preclude the demonstration that CT-P41 is highly similar to US-licensed Prolia and US-licensed Xgeva.
N-terminal pyroglutamate	Lower values were observed in CT-P41 HC and LC (0.6-1.1% and 0.2-0.3%, respectively) compared to US-licensed Prolia (1.3-1.7% and 0.3-0.5%, respectively). Similar differences were also observed between CT-P41 vial DP and US-licensed Xgeva lots. This

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	modification is not located in the antigen binding region or FcR binding region, no impact on biologic activity or PK is expected. Overall, the observed differences in N-terminal pyroglutamate variant results are minor and do not preclude the demonstration that CT-P41 is highly similar to US-licensed Prolia and US-licensed Xgeva.
C-terminal variants	Lower values of HC Lys448 (0.5-1.0%) and HC Lys448a (C-terminal Lys clipped, 88.8-97.7%) were observed in CT-P41 compared to US-licensed Prolia (0.9-1.8 % and 98.1-99.0%, respectively), associated with higher levels of HC Pro446 amidation (1.6-10.4%) in CT-P41 compared to US-licensed Prolia (0.1-0.2 %). Similar differences were also observed between CT-P41 vial DP and US-licensed Xgeva lots. C-terminal lysine residues are removed enzymatically in vivo. HC Pro446 amidation had no impact on biological activities as demonstrated by the CAA results. Therefore, differences in the amount of C-terminal variants do not preclude the demonstration that CT-P41 is highly similar to US- licensed Prolia and US-licensed Xgeva.
Glycation	Broader ranges were observed in both LC and HC of CT-P41 (0.9-6.0% and 2.6-7.0%, respectively) compared to US-licensed Prolia (3.4-4.2% and 5.9-7.0%, respectively). In addition, lower mean values were observed in both LC and HC of CT-P41 (1.5% and 3.4%, respectively) compared to US-licensed Prolia (3.8% and 6.3%, respectively). Similar differences were also observed between CT-P41 vial DP and US-licensed Xgeva lots. Only one of the 16 lysine residues (HC K65) is present in the CDR and located at the edge of CDR2, which is unlikely to be critical for binding to RANKL. The relatively lower level of glycation in CTP41 is unlikely to interfere with binding to RANKL, which was demonstrated by the bioactivity comparison in the CAA. Therefore, no impact on safety or efficacy is expected. Overall, the observed differences in glycation results do not preclude the demonstration that CT-P41 is highly similar to US-licensed Prolia and US-licensed Xgeva.
Methionine oxidation	Oxidized species were selected for an evaluation based on their impact and susceptibility to oxidation. Lower values were observed in oxidized HC Met253 (2.9-3.7%) compared to the levels detected in US-licensed Prolia (4.7-6.6%). HC Met253 oxidation could potentially impact antigen binding and FcRn binding. However, no differences in RANKL and FcRn binding were detected as part of CAA. Slightly lower levels of oxidized HC Met398 were also observed in CT-P41, i.e., 0.4-0.5% compared to 0.7-0.9% in US-licensed Prolia. The difference is very minor (approx. 0.3% difference by mean values). Similar differences were also observed between CT-P41 vial DP and

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	US-licensed Xgeva lots. Overall, the observed differences in Methionine oxidation results are minor and do not preclude the demonstration that CT-P41 is highly similar to US-licensed Prolia and US-licensed Xgeva.
IgG2 isoforms/Disulfide isoforms	Slightly higher values of disulfide isoform IgG2-A/B were observed in CT-P41 (10.85-17.65%, mean: 14.15%) compared to US-licensed Prolia (10.20-14.73%, mean: 13.38%) by RP-UPLC. This is associated with lower levels of IgG2-A1 (9.08-11.16%, mean: 9.93%) and IgG2-A2 (7.74-8.69%, mean: 8.21%) in CT-P41 compared to US-licensed Prolia (9.41-11.19%/ mean: 10.32% and 8.81-9.33%/mean: 9.08%, respectively). Similar differences were also observed between CT-P41 vial DP and US-licensed Xgeva lots. The magnitude of differences observed are minor and is not anticipated to impact safety, efficacy, or immunogenicity. Overall, the observed differences in IgG2 isoforms/ disulfide isoforms do not preclude the demonstration that CT-P41 is highly similar to US-licensed Prolia and US-licensed Xgeva.

E. Residual Uncertainties Assessment

Not applicable.

F. Same Strength(s)

CT-P41 prefilled syringe has the same dosage form and route of administration as US-licensed Prolia. Celltrion is seeking approval of 60 mg/mL CD-P41 solution in a 1 mL prefilled syringe as an interchangeable biosimilar to US-licensed Prolia is available at this strength. Comparative CT-P41 concentration (mg/mL) was assessed as part of the comparative analytical assessment. The extractable volume and fill weight data were also assessed in the context of manufacturing control. Based on similarity and manufacturing data, the 60 mg/mL CT-P41 in 1 mL prefilled syringe have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US-Prolia. The strength of CT-P41 prefilled syringe is the same as that of US-licensed Prolia. These presentations meet the statutory “same strength” requirement under Section 351 (k)(2)(A)(i)(IV) of the PHS Act.

CT-P41 vial has the same dosage form and route of administration as US-licensed Xgeva, but has a different formulation. Celltrion is seeking approval of 120 mg/1.7mL CT-P41 in a vial as an interchangeable biosimilar to US-licensed Xgeva. US-licensed

Xgeva is available at this strength (120mg/1.7mL) in a vial[1]. Celltrion is seeking approval of CT-P41 vial for the same strength as US-licensed Xgeva. Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment. The deliverable volume (mL) and fill weight data were assessed as part of manufacturing process controls. The strength of CT-P41 vial is the same as that of US-licensed Xgeva.

[1] U.S. Prescribing Information, U.S.-Licensed [Reference Product Proprietary Name]. Accessed [Date] from https://www.accessdata.fda.gov/scripts/cder/daf/

Yetao Jin

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