

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761400Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA 761400 Resubmission OPQ Executive Summary Addendum Assessment Date: June 2, 2025

Assessor comment: This addendum is being filed to document the updated agreed upon submission date for post-marketing commitment (PMC) 4848-2 of 07/2025.

1. Application/Product Information

BLA number	761400
Submission Type	Resubmission
Regulatory Pathway	NME 351 (a)
Associated IND/BLA	IND 138791
Review Designation	Priority Review
Applicant	Regeneron Pharmaceuticals, Inc.
Indication	Treatment of adult patients with relapsed or refractory multiple myeloma (b) (4) 
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Lynozyfic
	Non-proprietary Name/Code Name: livoseltamab-gcpt
	OBP Naming: MAB HUMAN (IGG4) ANTI Q02223 (TNR17_HUMAN) & ANTI P07766 (CD3E_HUMAN) [REGN5458]
Drug Product Description	Linvoseltamab-gcpt is an IgG4-based protein containing two identical human kappa light chains (LCs), each covalently linked to one of two unique human gamma heavy chains (HCs). The complementarity-determining regions (CDRs) within the HC1 variable domain bind to

	human B-cell maturation antigen (BCMA). The CDRs within the HC2 variable domain bind to human cluster of differentiation 3 (CD3). The linvoseltamab-gcpt drug product is an aqueous clear to slightly opalescent, colorless to pale yellow (b) (4) solution of pH 6.0 containing either 5 mg (2 mg/mL) or 200 mg (20 mg/mL) linvoseltamab-gcpt with (b) (4) mM L-Histidine, (b) (4) % Sucrose, (b) (4) % polysorbate 80, and water for injection (WFI). Both DP presentations are filled into a (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum seal cap.		
Dosage Form	Liquid		
Strength	5 mg linvoseltamab-gcpt per 2.5 mL (2 mg/mL) and 200 mg linvoseltamab-gcpt per 10.0 mL (20 mg/mL)		
Route of Administration	Intravenous (IV) injection		
Primary Container Closure System	Both presentations are filled in a (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum seal cap.		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	You (Joy) Zhuo	Brian Roelofs
	Drug product		
	Immunogenicity Assay		
	Facility	Jiangsong Jiang	Kamal Tiwari
	Microbiology	Reyes Candau-Chacon	Virginia Carroll
	RBPM	Kelly Ballard	

	ATL	Brian Roelofs
OPQ Issued Consults	N/A	

2. Recommendation and Conclusion on Approvability

Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761400 for LYNOZYFIC manufactured by Regeneron Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of LYNOZYFIC is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:** Regeneron Pharmaceuticals, Inc., Rensselaer, New York, United States, FEI: 1000514603
- **Drug Product:** (b) (4)
FEI: (b) (4)
- **Labeling/Packaging:** (b) (4)
FEI: (b) (4)

b. Fill size and dosage form: LYNOZYFIC is supplied as either a 5 mg (2 mg/mL) or 200 mg (20 mg/mL) solution in a single dose (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum seal cap.

c. Dating Period:

- **Drug Product:** 18 months at 5 ± 3°C, protected from light.
- **Drug Substance:** (b) (4) months at (b) (4) °C (b) (4)
- **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 drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes
- Rationale, if exempted: LYNOZYFIC is exempted from lot release per FR 95-29960.

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

4848-2

Develop and validate an SE-UPLC method with adequate resolving power to separate the intact linvoseltamab from known product-related impurities (aggregates and fragments).

Final Report Submission: 07/2025

4. Basis for Recommendation

a. Summary: Linozyfic (linvoseltamab-gcpt, REGN5458) is an IgG4-based bispecific protein containing two identical human kappa light chains (LCs), each covalently linked to one of two unique human gamma heavy chains (HCs). The complementarity-determining regions (CDRs) within the HC1 variable domain bind to human B-cell maturation antigen (BCMA). The CDRs within the HC2 variable domain bind to human cluster of differentiation 3 (CD3). The biological activity of linvoseltamab-gcpt is evaluated based on its ability to activate T-cells (b) (4) upon binding BCMA

The linvoseltamab-gcpt drug product (DP) is an aqueous clear to slightly opalescent, colorless to pale yellow (b) (4) solution of pH 6.0 containing either 5 mg (2 mg/2.5 mL vial) or 200 mg (20 mg/10 mL vial) linvoseltamab-gcpt with (b) (4) mM L-Histidine, (b) (4) % Sucrose, (b) (4) % polysorbate 80, and water for injection (WFI). Both DP presentations are filled into a (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum seal cap.

The potency of linvoseltamab-gcpt is assessed using a cell-based bioassay to measure the biological activity of T-cell activation upon BCMA binding. The bioassay uses (b) (4)

Linvoseltamab-gcpt drug substance (DS) is manufactured at Regeneron Pharmaceuticals, Inc., Rensselaer, New York, United States. (b) (4)

(b) (4)

Linvoseltamab-gcpt DP is manufactured (b) (4)

Data for the control of the purity of linvoseltamab-gcpt include the use of size exclusion ultra performance liquid chromatography (SE-UPLC). (b) (4)

(b) (4)

A post-marketing commitment was agreed to for the Applicant to optimize the SE-UPLC method because the DS and DP purity determined by SE-UPLC is informative to allow assessment for batch comparability regarding purity, as well as stability trending post licensure. (b) (4)

(b) (4)

The HMW, LMW and purity of linvoseltamab can be assessed by the current methods in the specifications; therefore, the optimization of SE-UPLC method can be completed post approval.

The assessment of manufacturing information provided in this application has concluded that the methodologies and processes used for DS and DP manufacturing, release, and stability testing are sufficiently robust and controlled to ensure the consistent manufacture of a safe, pure, and potent product. The assessment of the microbial control and sterility assurance strategy has concluded with a recommendation of approvable. The immunogenicity assays to detect and confirm anti-drug antibodies (ADAs) against livoseltamab-gcpt in the clinical studies to support this BLA were adequately validated and suitable for their intended purpose.

The pre-license inspection (PLI) of the DS manufacturing facility Regeneron Pharmaceuticals, Inc. (Rensselaer, NY, USA, FEI: 1000514603) was waived based on satisfactory inspection history.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for (b) (4) (FEI (b) (4)), proposed for livoseltamab-gcpt DP manufacture. The recent inspection covered the DP manufacturing site, (b) (4) and the outcome was reclassified as VAI. Therefore, the recommendation from the OPQ facilities perspective for livoseltamab-gcpt is for approval for this facility.

b. Subdiscipline Recommendation:

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

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 livoseltamab-gcpt i.e., there is no specific test method described in regulation for livoseltamab-gcpt that establishes an official standard of potency. We next considered whether potency is a factor for livoseltamab-gcpt 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 linvoseltamab-gcpt for purposes of § 610.61(r) because lot variability is not a concern for linvoseltamab-gcpt as linvoseltamab-gcpt’s manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Drug Substance:

- i. Protocols approved:
 - Qualification of a new WCB
 - Concurrent (b) (4) validation protocols (b) (4)
(b) (4)
 - Qualification protocols for new primary and working reference standards
 - (b) (4) protocol (b) (4)
(b) (4)
 - Drug substance annual stability protocol (with shelf-life extension)
- ii. Residual risk:
 - Refer to section 4.a of this memo for residual risks related to the optimization of the SE-UPLC chromatography method.
- iii. Future inspection points to consider: None

b. Drug Product:

- i. Protocols approved:
 - Leachable study protocol for drug product process performance qualification batches
 - Drug product annual stability protocol (with shelf-life extension)
- ii. Residual risk:
 - Refer to section 4.a of this memo for residual risks related to the optimization of the SE-UPLC chromatography method.
- iii. Future inspection points to consider: None

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.

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/

BRIAN A ROELOFS
06/11/2025 11:35:59 AM

LABELS AND LABELING ASSESSMENT

Date of Assessment:	May 20, 2025
Assessor:	Diana Pei, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	You Zhuo, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XIV
Application:	BLA 761400-ORIG-1-RESUB-79
Applicant:	Regeneron Pharmaceuticals, Inc.
Submission Date:	January 10, 2025
Product:	LYNOZYFIC (linvoseltamab-gcpt)
Dosage form(s):	Injection
Strength and Container-Closure:	5 mg/2.5 mL (2 mg/mL) single-dose vial 200 mg/10 mL (20 mg/mL) single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for the approval of LYNOZYFIC (linvoseltamab-gcpt) for the treatment of adult patients with relapse or refractory multiple myeloma (b) (4) (b) (4) (b) (4) (b) (4)
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 May 19, 2025 and container labels, and carton labeling submitted on March 17, 2025 were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on February 7, 2025)
<\\CDSESUB1\EVSPROD\bla761400\0055\m1\us\114-labeling\draft\labeling\proposed-uspi.docx>
- Medication Guide (submitted on February 11, 2025)
<\\CDSESUB1\EVSPROD\bla761400\0056\m1\us\114-labeling\draft\labeling\med-guide.docx>
- Container Labels (submitted on June 3, 2024)

(b) (4)

2 Pages 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 Labeling³ Standards

Container⁴ 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
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (U.S license number for container bearing a partial label^f)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Lot number or other lot identification (container label)	Acceptable

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 21 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."

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)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<i>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)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

Product Strength (container label)	Acceptable
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>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</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

Statement: "Rx only" (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>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)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Medication Guide (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: The label is small and would be considered a partial label. Thus, a Medication Guide statement is not required per 21 CFR 610.60(a)(7).

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
<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☒ Yes ☐ No ☐ N/A

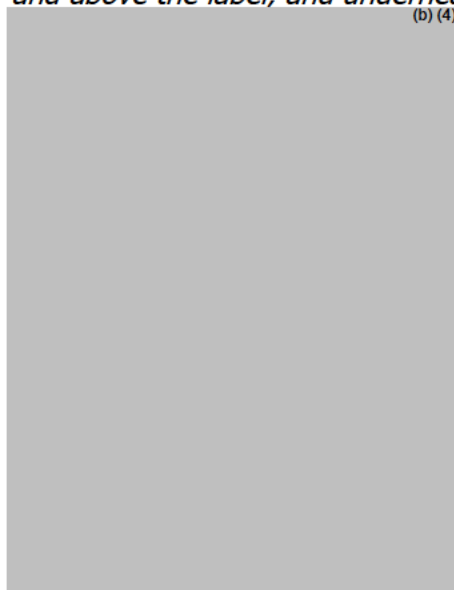
Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials.

Regeneron confirms that no text is present 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.

Regeneron confirms that the vial remains uncovered for the full length to allow for visual inspection when the label is affixed to the vial. There is a sufficient area of the container that remains uncovered to allow for visual inspection when the label is affixed to the container. Figure A illustrates the full circumference uncovered between the bottom of the container and the bottom of the label. Figure B illustrates the full length of container uncovered, beneath and above the label, and underneath the clear label overwrap.



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
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

NDC numbers (container label)	Acceptable

Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

Package type term (container label)	Acceptable
<i>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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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
<i>Recommended labeling practices references: Guidance for Industry Bar Code Label Requirements Questions and Answers (August 2011)</i> <i>Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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 label is small and could be considered a partial label. Thus, a dosage statement is not required.

Inactive ingredients (container label)	Acceptable
Regulation: 21 CFR 201.100, FD&C Act section 502(e)	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☐ 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.

Storage requirements (container label)	Acceptable
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The label is small and could be considered a partial label. Thus, storage information is not required.

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

Comment/Recommendation:

Package⁶ Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2), 21 CFR 600.3(k)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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
<i>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</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	Acceptable
Regulation: 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

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
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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:

Inactive ingredients (package labeling)	Acceptable
Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

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 lincoseltamab products (i.e., there is no specific test method described in regulation for lincoseltamab 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 Lynozytic 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.

The applicant did not propose to include a "No U.S. standard of potency" statement on the carton. Thus, no comment will be sent to the applicant.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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 <i>Bar Code Label Requirements Questions and Answers</i> (August 2011) Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

NDC numbers (package labeling)	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Preparation instructions (package labeling)	Acceptable
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A

<i>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</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Package type term (package labeling)	Acceptable
<i>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</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Statement of Dosage (package labeling)	Acceptable
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

Other (package labeling)	Acceptable
	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
<i>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</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

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
<i>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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable
Regulation: 21 CFR 201.57(c)(3)(iv) <i>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."</i>	☒ Yes ☐ No ☐ N/A
<i>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</i> <i>Draft Guidance Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2023)</i>	☒ 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.

The compatibility study uses an in-line filter. There is no data to support not using an in-line filter. Thus, the wording has been changed to require using an in-line filter
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
<i>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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:
 We added the pharmacological class per 21 CFR 201.57(c)(12)(i)(E).
The Applicant revised as requested.

We removed clinical pharmacology related information from this section of labeling.
The Applicant revised as requested.

Full Prescribing Information	
15 & 16 Hazardous Drug	Acceptable
Regulation: 21 CFR 201.57(c)(17)(iv)	☐ Yes ☐ No ☒ N/A
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	

Comment/Recommendation:

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
Regulation: 21 CFR 201.57(c)(17)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
 We revised to indicate the packaging configuration for the How Supplied aspect.
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
<i>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)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:
 The form FDA 356h does not include a period after "Inc" whereas your labeling includes a period after the "Inc.". Ensure that the manufacturer name matches exactly as it is written in Line 2 of the form FDA 356h including punctuation. If necessary, correct this on your form FDA 356h.
The Applicant revised as requested.

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

Comment/Recommendation:

MEDICATION GUIDE

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

Comment/Recommendation:

MEDICATION GUIDE	
INGREDIENTS	Acceptable
<i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:
 The inactive ingredients are not ordered in alphabetical order. Reorder the inactive ingredients so they are listed as: histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose, and Water for Injection. Per USP General Chapters <1091> Labeling of Inactive Ingredients.

The Applicant revised as requested.

MEDICATION GUIDE	
MANUFACTURER INFORMATION	Acceptable
21 CFR 208.20(b)(8)(iii)	☒ Yes ☐ No ☐ N/A
<i>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)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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 (submitted on May 19, 2025)
<\\CDSESUB1\EVSPROD\bla761400\0063\m1\us\114-labeling\draft\labeling\proposed-uspi.docx>

- Medication Guide (submitted on May 19, 2025)
<\\CDSESUB1\EVSPROD\bla761400\0063\m1\us\114-labeling\draft\labeling\proposed-med-guide.docx>
- Container Labels (submitted on March 17, 2025)



(b) (4)

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



Diana
Pei

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You
Zhuo

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BLA 761400 Resubmission OPQ Executive Summary
Assessment Date: May 23, 2025

1. Application/Product Information

BLA number	761400
Submission Type	Resubmission
Regulatory Pathway	NME 351 (a)
Associated IND/BLA	IND 138791
Review Designation	Priority Review
Applicant	Regeneron Pharmaceuticals, Inc.
Indication	Treatment of adult patients with relapsed or refractory multiple myeloma (b) (4)
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Lynozyfic
	Non-proprietary Name/Code Name: livoseltamab-gcpt
	OBP Naming: MAB HUMAN (IGG4) ANTI Q02223 (TNR17_HUMAN) & ANTI P07766 (CD3E_HUMAN) [REGN5458]
Drug Product Description	Linvoseltamab-gcpt is an IgG4-based protein containing two identical human kappa light chains (LCs), each covalently linked to one of two unique human gamma heavy chains (HCs). The complementarity-determining regions (CDRs) within the HC1 variable domain bind to human B-cell maturation antigen (BCMA). The CDRs within the HC2 variable domain bind to human cluster

	of differentiation 3 (CD3). The livoseltamab-gcpt drug product is an aqueous clear to slightly opalescent, colorless to pale yellow (b) (4) solution of pH 6.0 containing either 5 mg (2 mg/mL) or 200 mg (20 mg/mL) livoseltamab-gcpt with (b) (4) mM L-Histidine, (b) (4) % Sucrose, (b) (4) % polysorbate 80, and water for injection (WFI). Both DP presentations are filled into a (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum seal cap.		
Dosage Form	Liquid		
Strength	5 mg livoseltamab-gcpt per 2.5 mL (2 mg/mL) and 200 mg livoseltamab-gcpt per 10.0 mL (20 mg/mL)		
Route of Administration	Intravenous (IV) injection		
Primary Container Closure System	Both presentations are filled in a (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum seal cap.		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	You (Joy) Zhuo	Brian Roelofs
	Drug product		
	Immunogenicity Assay		
	Facility	Jiangsong Jiang	Kamal Tiwari
	Microbiology	Reyes Candau-Chacon	Virginia Carroll
	RBPM	Kelly Ballard	
	ATL	Brian Roelofs	

OPQ Issued Consults	N/A

2. Recommendation and Conclusion on Approvability

Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761400 for LYNOZYFIC manufactured by Regeneron Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of LYNOZYFIC is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:** Regeneron Pharmaceuticals, Inc., Rensselaer, New York, United States, FEI: 1000514603

- **Drug Product:** (b) (4)
FEI: 1 (b) (4)

- **Labeling/Packaging:** (b) (4)
(b) (4) FEI: (b) (4)

- **Fill size and dosage form:** LYNOZYFIC is supplied as either a 5 mg (2 mg/mL) or 200 mg (20 mg/mL) solution in a single dose (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum seal cap.

c. Dating Period:

- **Drug Product:** 18 months at 5 ± 3°C, protected from light.
- **Drug Substance:** (b) (4) months at (b) (4) °C (b) (4)
- **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 drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes
- Rationale, if exempted: LYNOZYFIC is exempted from lot release per FR 95-29960.

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

4848-2

Develop and validate an SE-UPLC method with adequate resolving power to separate the intact linvoseltamab from known product-related impurities (aggregates and fragments).

4. Basis for Recommendation

a. Summary: Lynozytic (linvoseltamab-gcpt, REGN5458) is an IgG4-based bispecific protein containing two identical human kappa light chains (LCs), each covalently linked to one of two unique human gamma heavy chains (HCs). The complementarity-determining regions (CDRs) within the HC1 variable domain bind to human B-cell maturation antigen (BCMA). The CDRs within the HC2 variable domain bind to human cluster of differentiation 3 (CD3). The biological activity of linvoseltamab-gcpt is evaluated based on its ability to activate T-cells (b) (4) upon binding BCMA

The linvoseltamab-gcpt drug product (DP) is an aqueous clear to slightly opalescent, colorless to pale yellow (b) (4) solution of pH 6.0 containing either 5 mg (2 mg/2.5 mL vial) or 200 mg (20 mg/10 mL vial) linvoseltamab-gcpt with (b) (4) mM L-Histidine, (b) (4) % Sucrose, (b) (4) % polysorbate 80, and water for injection (WFI). Both DP presentations are filled into a (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum seal cap.

The potency of linvoseltamab-gcpt is assessed using a cell-based bioassay to measure the biological activity of T-cell activation upon BCMA binding. The bioassay uses (b) (4)

Linvoseltamab-gcpt drug substance (DS) is manufactured at Regeneron Pharmaceuticals, Inc., Rensselaer, New York, United States. (b) (4)

[REDACTED] (b) (4)

Linvoseltamab-gcpt DP is manufactured [REDACTED] (b) (4)

Data for the control of the purity of linvoseltamab-gcpt include the use of size exclusion ultra performance liquid chromatography (SE-UPLC). [REDACTED] (b) (4)

[REDACTED] A post-marketing commitment was agreed to for the Applicant to optimize the SE-UPLC method because the DS and DP purity determined by SE-UPLC is informative to allow assessment for batch comparability regarding purity, as well as stability trending post licensure. [REDACTED] (b) (4)

[REDACTED] The HMW, LMW and purity of linvoseltamab can be assessed by the current methods in the specifications; therefore, the optimization of SE-UPLC method can be completed post approval.

The assessment of manufacturing information provided in this application has concluded that the methodologies and processes used for DS and DP

manufacturing, release, and stability testing are sufficiently robust and controlled to ensure the consistent manufacture of a safe, pure, and potent product. The assessment of the microbial control and sterility assurance strategy has concluded with a recommendation of approvable. The immunogenicity assays to detect and confirm anti-drug antibodies (ADAs) against linvoseltamab-gcpt in the clinical studies to support this BLA were adequately validated and suitable for their intended purpose.

The pre-license inspection (PLI) of the DS manufacturing facility Regeneron Pharmaceuticals, Inc. (Rensselaer, NY, USA, FEI: 1000514603) was waived based on satisfactory inspection history.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for (b) (4) (FEI (b) (4)), proposed for linvoseltamab-gcpt DP manufacture. The recent inspection covered the DP manufacturing site, (b) (4) and the outcome was reclassified as VAI. Therefore, the recommendation from the OPQ facilities perspective for linvoseltamab-gcpt is for approval for this facility.

b. Subdiscipline Recommendation:

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

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 linvoseltamab-gcpt i.e., there is no specific test method described in regulation for linvoseltamab-gcpt that establishes an official standard of potency. We next considered whether potency is a factor for linvoseltamab-gcpt 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 linvoseltamab-gcpt for purposes of § 610.61(r) because lot variability is not a concern for linvoseltamab-gcpt as

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

5. Life-Cycle Considerations

a. Drug Substance:

- i. Protocols approved:
 - Qualification of a new WCB
 - Concurrent (b) (4) validation protocols (b) (4)
(b) (4)
 - Qualification protocols for new primary and working reference standards
 - (b) (4) protocol (b) (4)
(b) (4)
 - Drug substance annual stability protocol (with shelf-life extension)
- ii. Residual risk:
 - Refer to section 4.a of this memo for residual risks related to the optimization of the SE-UPLC chromatography method.
- iii. Future inspection points to consider: None

b. Drug Product:

- i. Protocols approved:
 - Leachable study protocol for drug product process performance qualification batches
 - Drug product annual stability protocol (with shelf-life extension)
- ii. Residual risk:
 - Refer to section 4.a of this memo for residual risks related to the optimization of the SE-UPLC chromatography method.
- iii. Future inspection points to consider: None

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.

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/

BRIAN A ROELOFS
05/23/2025 11:52:01 AM

PRODUCT QUALITY MICROBIOLOGY ASSESSMENT

Application ID	BLA 761400-0051 resubmission
Submission Type	Original BLA
Drug Product Name	Linvoseltamab-gctp (REGN5458), LYNOZYFIC
Strengths	2 mg/mL and 20 mg/mL
Dosage Form	Sterile solution for Injection
Administration Route	Intravenous infusion
Indication	Relapsed or refractory multiple myeloma (b) (4)
Applicant Name	Regeneron Pharmaceuticals, Inc
US License Number	1760
Application Type	351 (a)
Primary Reviewer	Reyes Candau-Chacon, PhD
Secondary Reviewer	Virginia Carroll, PhD
Goal Date	July 10, 2025

Recommendation for Approvability:

- This BLA resubmission was reviewed from a product quality microbiology perspective and sterility assurance perspective and it is recommended for approval.
- Refer to Panorama for the Manufacturing Facility Assessment Recommendation (approval).
- Product quality aspects not related to microbial control and facilities should be reviewed by OPQA.

Summary Basis of Recommendation (DS):

Overall, the process is under adequate microbial control. Microbial quality is controlled at each step of the manufacturing process (b) (4)

(b) (4) Bioburden and endotoxin samples are monitored at each critical step of the manufacturing process and at DS release. Microbial control (b) (4) was demonstrated (b) (4)

(b) (4) Adequate controls are in place to maintain microbiological product quality (b) (4) throughout the manufacturing process.

Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management:

CQA (type)	Risk	Origin	Control Strategy	Other
Endotoxin	Safety, Purity	Raw materials, manufacturing process	(b) (4)	
Bioburden	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials, manufacturing process	(b) (4)	

Summary Basis of Recommendation (DP):

All sterile drug product-contact equipment and components are sterilized and depyrogenated using validated processes. The drug product is sterilized (b) (4)

Bioburden and endotoxin are tested during manufacture, and sterility and endotoxin are tested at release. Container closure integrity testing using a validated method is included in the stability program.

Drug Product CQA Process Risk Identification and Lifecycle Knowledge Management:

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (Contaminant)	Safety, Purity, and Efficacy	Manufacturing process, failure of the container closure integrity	(b) (4)	
Endotoxin (Contaminant)	Safety, Purity	Raw materials, manufacturing process		
Container closure integrity (Sterility assurance)	Safety (Sterility assurance)	Breach during manufacture or storage		

List Submissions being assessed:

Amendment #	Document description	Date Received
0051	Response to the CR letter	January 10, 2025

Application Submission Background

BLA 761400 was submitted on December 22, 2023 for the licensure of linvoseltamab for the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4)

The BLA was granted Orphan Drug Designation on June 6, 2022 and fast-track designation on March 30, 2023 and included references to IND 138791 for the treatment of hematological malignancies.

BLA 761400 received a Complete Response Letter on August 20, 2024 due to the facility inspection at (b) (4) (FEI: (b) (4)). The following Microbiology Additional Comment was included in the Complete Response Letter:

(b) (4)

BLA 761400/0051 (resubmission); Regeneron Pharmaceuticals, Inc.; lincoseltamab-gctp (REGN5458)

This memo covers the response to the microbiology additional comment. Information included in the submission of the original BLA was already reviewed and considered acceptable and is not reviewed here.

MODULE 3.2.P

P.3 Manufacture

(b) (4)



SATISFACTORY



Reyes
Candau-Chacon

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Virginia
Carroll

Digitally signed by Virginia Carroll
Date: 3/25/2025 03:00:16PM
GUID: 5898c0190049a524b6af8a93d389a1c0

BLA Executive Summary Addendum
Assessment Date: July 17, 2024

1. Application/Product Information

BLA number	761400
Submission Type	Original Submission
Regulatory Pathway	NME 351 (a)
Associated IND/BLA	IND 138791
Review Designation	Priority Review
Applicant	Regeneron Pharmaceuticals, Inc.
Indication	Treatment of adult patients with relapsed or refractory multiple myeloma (b) (4)
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Lynozyfic
	Non-proprietary Name/Code Name: livoseltamab- (b) (4)
	OBP Naming: BSMAB: MAB HUMAN (IGG4) ANTI Q02223 (TNR17_HUMAN) & ANTI P07766 (CD3E_HUMAN) [REGN5458]
Drug Product Description	Linvoseltamab is an IgG4-based protein containing two identical human kappa light chains (LCs), each covalently linked to one of two unique human gamma heavy chains (HCs). The complementarity-determining regions (CDRs) within the HC1 variable domain bind to human B-cell maturation antigen (BCMA). The CDRs within the HC2 variable domain bind to human cluster of differentiation 3 (CD3).

	The livoseltamab drug product (DP) is an aqueous clear to slightly opalescent, colorless to pale yellow (b) (4) solution of pH 6.0 containing either 5 mg (2 mg/mL) or 200 mg (20 mg/mL) livoseltamab with (b) (4) mM L-Histidine, (b) (4) % Sucrose, (b) (4) % polysorbate 80, and water for injection (WFI). Both DP presentations are filled into a (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum seal cap.		
Dosage Form	Liquid		
Strength	5 mg livoseltamab per 2.5 mL (2 mg/mL) and 200 mg livoseltamab per 10.0 mL (20 mg/mL)		
Route of Administration	Intravenous (IV) injection		
Primary Container Closure System	Both presentations are filled in a (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum seal cap.		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	You (Joy) Zhuo	Brian Roelofs
	Drug product		
	Immunogenicity Assay		
	Facility	Michael Shanks	Virginia Carroll
	Microbiology	Maria (Reyes) Candauchacon	
	RBPM	Kelly Ballard	
	ATL	Brian Roelofs	
OPQ Issued Consults	N/A		

2. Recommendation and Conclusion on Approvability

Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761400 for LYNOZYFIC manufactured by Regeneron Pharmaceuticals, Inc.. The data submitted in this application are not sufficient to support a conclusion that the manufacture of LYNOZYFIC is well-controlled and will lead to a product that is pure and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Regeneron Pharmaceuticals, Inc., to outline the deficiencies noted below and the information and data that will be required to support approval.

3. Draft Complete Response Comments and Additional Comments (if applicable):

Complete Response Comment:

1. During a recent inspection of (b) (4) (FEI: (b) (4)), listed in this application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response to your application. Your complete response should include the date(s) of the facility's response to the FDA Form 483. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

Additional Comments:

Product Quality

1. You assess size-based product-related impurities using an SE-UPLC method. (b) (4)
To ensure the suitability of the SE-UPLC method to characterize the purity of livoseltamab (b) (4) and drug product, you should optimize the SE-UPLC method with adequate resolving power to separate the intact livoseltamab from known product-related impurities (aggregates and fragments).

Product Quality Microbiology

2. (b) (4)

(b) (4)
Provide
data in your resubmission (b) (4) conducted with the
sterile product-contact equipment and container closure specific to each
linvoseltamab presentation (b) (4)

4. Basis for Recommendation

- a. Summary:** Lynozyfic (linvoseltamab- (b) (4) REGN5458) is an IgG4-based bispecific protein containing two identical human kappa light chains (LCs), each covalently linked to one of two unique human gamma heavy chains (HCs). The complementarity-determining regions (CDRs) within the HC1 variable domain bind to human B-cell maturation antigen (BCMA). The CDRs within the HC2 variable domain bind to human cluster of differentiation 3 (CD3). The biological activity of linvoseltamab is evaluated based on its ability to activate T-cells (b) (4) upon binding BCMA (b) (4)
(b) (4)

The linvoseltamab drug product (DP) is an aqueous clear to slightly opalescent, colorless to pale yellow (b) (4) solution of pH 6.0 containing either 5 mg (2 mg/2.5 mL vial) or 200 mg (20 mg/10 mL vial) linvoseltamab with (b) (4) mM L-Histidine, (b) (4) % Sucrose, (b) (4) % polysorbate 80, and water for injection (WFI). Both DP presentations are filled into a (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum seal cap.

The assessment of manufacturing information provided in this application has concluded that the methodologies and processes used for drug substance (DS) and DP manufacturing, release, and stability testing are sufficiently robust and controlled to ensure the consistent manufacture of a safe, pure, and potent product. The assessment of the microbial control and sterility assurance strategy has concluded with a recommendation of approvable. The immunogenicity assays to detect and confirm anti-drug antibodies (ADAs) against linvoseltamab in the clinical studies to support this BLA were adequately validated and suitable for their intended purpose.

The pre-license inspection (PLI) of the DS manufacturing facility Regeneron Pharmaceuticals, Inc. (Rensselaer, NY, USA, FEI: 1000514603) was waived based on satisfactory inspection history. The PLI of the linvoseltamab DP manufacturing facility (b) (4)
(b) (4) FEI: (b) (4)) was not performed, as an inspection of the same line proposed for commercial manufacture of linvoseltamab was performed in

support of another application and concluded with a recommendation of withhold approval. The internal compliance review of the firm's responses confirmed this recommendation. Refer to the facility review assessment memorandum and recommendation uploaded to Panorama on May 15, 2024. Therefore, the recommendation for BLA 761400 from OPQ is for a complete response for BLA 761400 with additional comments for product quality and product quality microbiology. Individual assessments for each discipline are located in separate documents in Panorama.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Immunogenicity Assay	-	Adequate
Facilities	-	Inadequate
Microbiology	-	Adequate

Comment: Items identified as post-marketing commitments (PMCs) previously will be included as additional comments in the action letter.

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.

5. 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.

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/

BRIAN A ROELOFS
07/17/2024 04:57:45 PM

VIRGINIA A CARROLL
07/17/2024 04:59:35 PM

ADDENDUM TO PRODUCT QUALITY MICROBIOLOGY ASSESSMENT

Application ID	BLA 761400/0
Submission Type	Original BLA
Drug Product Name	livoseltamab (REGN5458)
Strengths	2 mg/mL and 20 mg/mL
Dosage Form	Sterile solution for Injection
Administration Route	Intravenous infusion
Indication	Relapsed or refractory multiple myeloma (b) (4)
Applicant Name	Regeneron Pharmaceuticals, Inc
US License Number	1760
Application Type	351 (a)
Primary Reviewer	Reyes Candau-Chacon, PhD
Secondary Reviewer	Virginia Carroll, PhD
Goal Date	August 22, 2024 (PDUFA date)

Recommendation for Approvability:

- This BLA was reviewed from a product quality microbiology perspective and sterility assurance perspective and it is recommended for approval with the following additional comment included in the Complete Response Letter:

(b) (4)

- Refer to Panorama for the Manufacturing Facility Assessment Recommendation (withhold).
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

Application Submission Background

Regeneron has submitted amendment 0042 on June 21, 2024 to provide sterilization validation data (b) (4) in worst-case locations on three runs. This information was requested in FDA information requests sent on April 18, 2024 and May 16, 2024.

MODULE 3.2.P

P.3 Manufacture

(b) (4)



SATISFACTORY



Reyes
Candau-Chacon

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Virginia
Carroll

Digitally signed by Virginia Carroll
Date: 7/03/2024 09:25:19AM
GUID: 5898c0190049a524b6af8a93d389a1c0

PRODUCT QUALITY MICROBIOLOGY ASSESSMENT

Application ID	BLA 761400
Submission Type	Original BLA
Drug Product Name	livoseltamab (REGN5458)
Strengths	2 mg/mL and 20 mg/mL
Dosage Form	Sterile solution for Injection
Administration Route	Intravenous infusion
Indication	Relapsed or refractory multiple myeloma (b) (4)
Applicant Name	Regeneron Pharmaceuticals, Inc
US License Number	1760
Application Type	351 (a)
Primary Reviewer	Reyes Candau-Chacon, PhD
Secondary Reviewer	Virginia Carroll, PhD
Goal Date	August 22, 2024 (PDUFA date)

Recommendation for Approvability:

- This BLA was reviewed from a product quality microbiology perspective and sterility assurance perspective and its recommendation is PENDING the following information:

Data to demonstrate sterilization validation (b) (4) in worst-case locations. Interim results from the first run will be submitted by June 21, 2024 and the validation report from three runs will be submitted by July 22, 2024. An addendum to this memo will be uploaded in Panorama with the review of the applicant response and the Microbiology and Sterility Assurance recommendation.

The following additional comment should be included in the Complete Response Letter:

(b) (4)

- Refer to Panorama for the Manufacturing Facility Assessment Recommendation (withhold).
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

Summary Basis of Recommendation (DS):

Overall, the process is under adequate microbial control. Microbial quality is controlled at each step of the manufacturing process (b) (4)

(b) (4)

Adequate controls are in place to maintain microbiological product quality (b) (4) throughout the manufacturing process.

Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management:

CQA (type)	Risk	Origin	Control Strategy	Other
Endotoxin	Safety, Purity	Raw materials, manufacturing process	(b) (4)	
Bioburden	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials, manufacturing process		

Summary Basis of Recommendation (DP):

All sterile drug product-contact equipment and components are sterilized and depyrogenated using validated processes. The drug product is sterilized (b) (4)

Bioburden and endotoxin are tested during manufacture, and sterility and endotoxin are tested at release. Container closure integrity testing using a validated method is included in the stability program.

Drug Product CQA Process Risk Identification and Lifecycle Knowledge Management:

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (Contaminant)	Safety, Purity, and Efficacy	Manufacturing process, failure of the container closure integrity	(b) (4)	
Endotoxin (Contaminant)	Safety, Purity	Raw materials, manufacturing process		
Container closure integrity (Sterility assurance)	Safety (Sterility assurance)	Breach during manufacture or storage		

List Submissions being assessed:

Amendment #	Document description	Date Received
0001	Original BLA submission	December 22, 2023
0022	Response to IR1 sent on March 19, 2024	April 5, 2022
0028	Response to IR2 sent on April 18, 2024	April 25, 2024
0036	Response to IR3 sent on May 16, 2024	May 22, 2024

List of DMFs:

DMF #	Description	Finding	Document Reference	Review date
	(b) (4)	Adequate	D (b) (4) M41R01	March 8, 2022

Application Submission Background

Regeneron has submitted BLA 761400 for the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4). The BLA was granted Orphan Drug Designation on June 6, 2022 and fast-track designation on March 30, 2023. The BLA includes references to IND 138791 for the treatment of hematological malignancies.

MODULE 1

1.14 LABELING

Livoseltamab is provided in two dosage forms:

- 5 mg/2.5 mL (2 mg/mL) single-dose vial.
- 200 mg/10 mL (20 mg/mL) single-dose vial

2. Dosage and Administration

2.2. Recommended Dosage and Administration

Treatment includes:

- Set-up dose 1: 5 mg on day 1, administer as a 4-hour infusion (b) (4)
- Set-up dose 2: 25 mg on day 8, administer as a 4-hour infusion (b) (4)
- Full dose: 200 mg weekly treatment (b) (4)

Dexamethasone IV may be administered 1 to 3 hours before the infusion in addition of oral antihistamines and acetaminophen 30 to 60 minutes before the infusion.

2.6 Preparation and Administration

The desired dose of the vial is transferred to an infusion bag containing 0.9% sodium chloride injection USP as follows (modified from Table (b) (4) :

(b) (4)

The infusion may be stored up to 25°C for NMT 8 hours from the preparation of the infusion or at 2 to 8°C for NMT 48 hours.

Reviewer's Comment: The allowed storage conditions are supported by microbiology challenge data included in Section P.2.6 of the BLA and reviewed in that section of this memo. The maximum endotoxin contribution of the highest dose is (b) (4) + (b) (4) = (b) (4) EU. Livoseltamab is indicated for adult patients; therefore, the maximum dose includes over a (b) (4)-fold safety margin for a 60-kg patient and a (b) (4) safety margin for a 45-kg worst-case patient over the USP safety threshold of (b) (4) EU/kg/hour.

MODULE 3.2.S

S.1 General Information

Livoseltamab (REGN5458) is a bispecific monoclonal antibody containing two identical human kappa light chains, each one linked to one human gamma heavy chain. Each heavy chain binds to the human B-cell maturation antigen (BCMA) or to the human cluster of differentiation 3 (CD3) through the heavy chains complementarity-determining regions (CDRs), bringing together BCMA-expressing cells with CD3+ T cells, which results in targeted killing of the BCMA-expressing cells by the T cells.

Livoseltamab molecular weight based on its primary structure is 145.80 kDa.

S.2 Manufacture

S.2.1 Manufacturer(s)

(b) (4)

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MODULE 3.2.P

P.1 Description and Composition of the Drug Product

The drug product is a sterile solution for intravenous (IV) administration provided in 2 presentations:

- 2.5 mL vials at 2 mg/mL and 5 mg of livoseltamab per vial
- 10 mL vials at 20 mg/mL and 200 mg of livoseltamab per vial

Livoseltamab is formulated in (b) (4) mM L-histidine, (b) (4) % (w/v) sucrose, and (b) (4) % (w/v) polysorbate 80, pH (b) (4) (for additional information on the product composition, refer to Table 1 of Section P.1). The product is sterile and free of preservatives and is filled in a (b) (4) clear glass vial with an elastomeric stopper and aluminum seal cap.

P.2 Pharmaceutical Development

Multiple documents are included in this section to support the manufacturing process. Only those that may facilitate the review of this document or may impact sterility assurance of the drug product are reviewed here.

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Candau-Chacon

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Virginia
Carroll

Digitally signed by Virginia Carroll
Date: 7/03/2024 09:24:59AM
GUID: 5898c0190049a524b6af8a93d389a1c0

BLA 761400 Executive Summary

Assessment Date: June 27, 2024

1. Application/Product Information

BLA number	761400
Submission Type	Original Submission
Regulatory Pathway	NME 351 (a)
Associated IND/BLA	IND 138791
Review Designation	Priority Review
Applicant	Regeneron Pharmaceuticals, Inc.
Indication	Treatment of adult patients with relapsed or refractory multiple myeloma (b) (4)
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Linozyfic
	Non-proprietary Name/Code Name: livoseltamab- (b) (4)
	OBP Naming: BSMAB: MAB HUMAN (IGG4) ANTI Q02223 (TNR17_HUMAN) & ANTI P07766 (CD3E_HUMAN) [REGN5458]
Drug Product Description	Livoseltamab is an IgG4-based protein containing two identical human kappa light chains (LCs), each covalently linked to one of two unique human gamma heavy chains (HCs). The complementarity-determining regions (CDRs) within the HC1 variable domain bind to human B-cell maturation antigen (BCMA). The CDRs within the HC2 variable domain bind to human cluster of differentiation 3 (CD3).

	The livoseltamab drug product (DP) is an aqueous clear to slightly opalescent, colorless to pale yellow (b) (4) solution of pH 6.0 containing either 5 mg (2 mg/mL) or 200 mg (20 mg/mL) livoseltamab with (b) (4) mM L-Histidine, (b) (4) % Sucrose, (b) (4) % polysorbate 80, and water for injection (WFI). Both DP presentations are filled into a (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum seal cap.		
Dosage Form	Liquid		
Strength	5 mg livoseltamab per 2.5 mL (2 mg/mL) and 200 mg livoseltamab per 10.0 mL (20 mg/mL)		
Route of Administration	Intravenous (IV) injection		
Primary Container Closure System	Both presentations are filled in a (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum seal cap.		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	You (Joy) Zhuo	Brian Roelofs
	Drug product		
	Immunogenicity Assay		
	Facility	Michael Shanks	Virginia Carroll
	Microbiology	Maria (Reyes) Candauchacon	
	RBPM	Kelly Ballard	
	ATL	Brian Roelofs	
OPQ Issued Consults	N/A		

2. Recommendation and Conclusion on Approvability

Recommendation: Pending

The Office of Pharmaceutical Quality (OPQ), CDER, recommendation on approvability of BLA 761400 for LYNOZYFIC manufactured by Regeneron Pharmaceuticals, Inc. is pending the final determination of the microbiology assessment. Additionally, a withhold approval recommendation has been made for the DP manufacturing facility (b) (4) (b) (4) FEI: (b) (4).

An addendum to this memo will be filed upon completion of the microbiology assessment of the data submitted by the Applicant on June 21, 2024.

3. Basis for Recommendation

a. Summary: Linozofic (linvoseltamab- (b) (4) REGN5458) is an IgG4-based bispecific protein containing two identical human kappa light chains (LCs), each covalently linked to one of two unique human gamma heavy chains (HCs). The complementarity-determining regions (CDRs) within the HC1 variable domain bind to human B-cell maturation antigen (BCMA). The CDRs within the HC2 variable domain bind to human cluster of differentiation 3 (CD3). The biological activity of linozofic is evaluation based on its ability to activate T-cells (b) (4) upon binding BCMA (b) (4).

The linozofic drug product (DP) is an aqueous clear to slightly opalescent, colorless to pale yellow (b) (4) solution of pH 6.0 containing either 5 mg (2 mg/2.5 mL vial) or 200 mg (20 mg/10 mL vial) linozofic with (b) (4) mM L-Histidine, (b) (4) % Sucrose, (b) (4) % polysorbate 80, and water for injection (WFI). Both DP presentations are filled into a (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum seal cap.

The assessment of manufacturing information provided in this application has concluded that the methodologies and processes used for drug substance (DS) and DP manufacturing, release, and stability testing are sufficiently robust and controlled to ensure the consistent manufacture of a safe, pure, and potent product. The assessment of the microbial and sterility assurance strategy and the ability to consistently manufacture a sterile product is ongoing. The pre-license inspection (PLI) of the DS manufacturing facility Regeneron Pharmaceuticals, Inc. (Rensselaer, NY, USA, FEI: 1000514603) was waived based on satisfactory inspection history. The PLI of the linozofic DP manufacturing facility (b) (4)

((b) (4) FEI: (b) (4)) was not performed as an inspection of the same line proposed for commercial manufacture of linvoseltamab was performed in support of another application and concluded with a recommendation of withhold approval. The internal compliance review of the firm's responses confirmed this recommendation. Refer to the facility review assessment memorandum and recommendation uploaded to Panorama on May 15, 2024. Therefore, the recommendation for BLA 761400 from an OPQ facilities perspective with regard to the DP manufacturing facility will be for withhold approval for BLA 761400.

b. Subdiscipline Recommendation:

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

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/

BRIAN A ROELOFS
06/27/2024 06:30:10 PM

VIRGINIA A CARROLL
06/27/2024 06:31:51 PM

OBP CMC Assessment Data Sheet

1. BLA#: STN 761400
2. Assessment Date: June 26, 2024
3. Primary Assessment Team:

Medical Officer		Deepti Telaraja / Bindu Kanapuru
Clinical Pharmacology		Banu Zolnik / Xiling Jiang
Pharm/Tox		Liz Garcia Peterson / Brenda Gehrke
Statistics		Jay Zhao / Lisa Rodriguez
DMEPA		Jody Kundreskas / Nicole Iverson
Product Quality Team	OBP Drug Substance, Drug Product, and Immunogenicity	You (Joy) Zhuo
	Drug Substance Microbiology/Facility	Maria Candauchacon
	Drug Product Microbiology/Facility	Michael Shanks
	Facility secondary	Virginia Carroll
	Micro Secondary	Virginia Carroll
	OBP Labeling	Diana Pei/Vicky Borders-Hemphill
	RBPM	Kelly Ballard
	Application Technical Lead	Brian Roelofs

4. Major GRMP Deadlines:
 - a. Filing Meeting (Internal): February 12, 2024
 - b. Filing date: February 20, 2024
 - c. Mid-cycle meeting (Internal): April 2, 2024 and April 9, 2024
 - d. Mid-cycle meeting (Sponsor): April 11, 2024
 - e. Late-Cycle meeting (Internal): May 28, 2024
 - f. Late-Cycle meeting (Sponsor): June 24, 2024
 - g. Primary assessment due: June 27, 2024
 - h. Wrap-up meeting: July 18, 2024
 - i. PDUFA action date: August 22, 2024

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Type C CMC only Pre-BLA Meeting	May 15, 2023
Type B pre-BLA meeting	October 18, 2023

Application Orientation Meeting	February 16, 2024
Mid-Cycle Meeting	April 11, 2024
Late-Cycle Meeting	June 24, 2024

6. Submission Assessed:

Submission:	Date Received:	Assessment Completed (yes or no):
Original BLA Submission (SDN 1)	December 22, 2023	Yes
Response to IR#1 (SDN 22/eCTD 0022)	April 5, 2024	Yes
Response to IR#2 (SDN 33/eCTD 0032)	May 9, 2024	Yes
Response to IR#3 (SDN 38/eCTD 0039)	June 3, 2024	Yes
Response to IR#4 (SDN 44/eCTD 0041)	June 12, 2024	Yes

7. Drug Product Name/Code/Type:

- a. Proprietary Name: Lynozyfic
- b. Trade Name: Lynozyfic
- c. Non-Proprietary Name/USAN: Linvoseltamab- (b) (4)
- d. CAS Name: 2408319-25-3
- e. Common Name: *Not Applicable*
- f. INN Name: Linvoseltamab
- g. Compendial Name: *Not Applicable*
- h. OBP systematic name: BSMAB: MAB HUMAN (IGG4) ANTI Q02223 (TNR17_HUMAN) & ANTI P07766 (CD3E_HUMAN) [REGN5458]
- i. Other names: REGN5458

Assessor's Note: According to the DMEPA 2 decision for the nonproprietary name suffix, the suffix (b) (4) is acceptable. The review comment was shared by the RPM via email on June 5, 2024. In the rest of the memo, "linvoseltamab" is used to refer to linvoseltamab (b) (4)

8. Pharmacological Category: Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager

9. Dosage Form: Injection

10. Strength/Potency:

(i) The concentration/strength of the Drug Product: 5 mg linvoseltamab per 2.5 mL (2 mg/mL) and 200 mg linvoseltamab per 10.0 mL (20 mg/mL)

(ii) Type of potency assay: A cell-based bioassay to measure the biological activity of T-cell activation upon BCMA binding is used for linvoseltamab drug substance and drug product

release and stability testing. The bioassay uses (b) (4)
(b) (4)

11. Route of Administration: Intravenous injection

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4) (Type V)	(b) (4)	(b) (4)	Yes	<i>No assessment required at this time as the relevant information related to compatibility with the product was in the BLA.</i>
(b) (4) (Type III)			Yes	
(b) (4) (Type III)			Yes	
(b) (4) (Type V)			Yes	<i>Sufficient information regarding drug product manufacturing was also submitted to module 3.2.P and 3.2.R for livoseltamab. Assessment deferred to OPMA.</i>

13. Inspectional Activities:

- Pre-license inspection (PLI) of the livoseltamab drug substance manufacturing facility (Regeneron Pharmaceuticals, Inc., 81 Columbia Turnpike, Rensselaer, NY, USA, 12144, FEI 1000514603) was waived. Refer to Site Inspection Determination finalized in Panorama on May 15, 2024.
- The PLI of the livoseltamab DP manufacturing facility (b) (4) (b) (4) (b) (4) FEI: (b) (4) was not performed as an inspection of the line proposed for commercial manufacture of livoseltamab was performed in support of (b) (4) and concluded with a recommendation of withhold approval. The internal compliance review of the firm's responses confirmed this recommendation. Therefore, the recommendation for BLA 761400 from an OPQ facilities perspective with regard to the drug product manufacturing facility will be for withhold approval for the facility and a complete response for BLA 761400.

14. Consults Requested by OBP: None

15. Quality by Design Elements:

The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. Precedents: None

17. Administrative:

Signature Block	
Name and Title	Signature and Date
You Zhuo, Ph.D. Primary Reviewer, CDER/OPQ/OPQA-III/DPQA-XIV	See electronic signature and date
Brian Roelofs, Ph.D. Application Technical Lead, CDER/OPQ/OPQA-III/DPQA-XIV	See electronic signature and date

Summary of Quality Assessments

I. Primary Assessor Summary Recommendation

II. List of Deficiencies to be Communicated

III. List of Post-Marketing Commitments/Requirements

Develop and validate an SE-UPLC method with adequate resolving power to separate the intact livoseltamab from known product-related impurities (aggregates and fragments).

Final report submission date: 06/2025

Assessor comment: *The Applicant also stated*

(b) (4)
(b) (4)

(b) (4) *While this language is not part of the commitment, the acknowledgement by the Applicant that additional studies of the potential impact of the*

(b) (4) *studies is acceptable. As noted below, there are*

(b) (4) *in the control strategy,*

(b) (4)

IV. List of Protocols

eCTD Sections	Protocol	Brief Summary	Reporting category
3.2.S.2.3 Protocol for Qualification of a new Working Cell Bank			(b) (4) Annual Reportable
3.2.S.2.5			Annual Reportable
3.2.S.2.5			Annual Reportable
3.2.S.2.5			Annual Reportable

3.2.S.2.5	(b) (4) Protocol	This protocol details the approach (b) (4) (b) (4) Performance data must meet all acceptance criteria to verify that the process is well-controlled.	Annual Reportable
3.2.S.5	Protocol for Qualification of a New Reference Standard	The protocol describes the analytical methods and acceptance criteria for qualification of future linsoseltamab primary and working reference standards.	Annual Reportable
3.2.S.5	Protocol for Requalification of a Reference Standard	The protocol describes the analytical methods and acceptance criteria for stability monitoring and requalification of linsoseltamab primary and working reference standards.	Annual Reportable
3.2.S.7.1	Shelf-life extension protocols	The linsoseltamab (b) (4) (b) (4) ongoing 60-month stability study.	Annual Reportable
3.2.S.7.2	Post-Approval Drug Substance Stability Protocol and Stability Commitment	(b) (4) (b) (4) The primary stability studies will be completed in accordance with the stability protocol.	Annual Reportable
3.2.P.2	Leachable study protocol for drug product PPQ batches manufactured (b) (4)	Regeneron commits to conduct 60-month real-time leachable studies for 5 mg and 200 mg drug product PPQ batches manufactured (b) (4)	Annual Reportable.
3.2.P.8.1	Shelf-life extension protocols	The drug product stability protocol for primary stability batches and PPQ batches includes time points 0, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54	Annual Reportable. The ongoing stability studies of supportive stability/process validation batches will be

		and 60 months. It is ongoing. As data become available for subsequent time points, the shelf life may be extended provided that all protocol acceptance criteria are met.	reported in the annual report.
3.2.P.8.2	Post-Approval Drug Product Stability Protocol and Stability Commitment	At least one batch of drug product at each registered presentation will be enrolled in post-approval commercial stability program each year that manufacturing occur(s) at the long-term storage condition with testing interval at initial, 3, 6, 9, 12, 18, 24, 36, 48, 60 months.	Annual Reportable

V. Assessment of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

Regeneron Pharmaceuticals, Inc. (Regeneron) requests a categorical exclusion from the preparation of an environmental assessment on the basis of 21 CFR 25.31(c) for the production of linvoseltamab. To Regeneron’s knowledge, no extraordinary circumstances exist.

Assessor’s comment: *Linvoseltamab is composed of proteins that are expected to be rapidly degraded to amino acids and mineralized to carbon dioxide by microbial activity. The Applicant’s assessment and claim of categorical exclusion from preparation of an environmental assessment are acceptable.*

VI. Primary Container Labeling Assessment

The OPQA-III assessment of the primary container labeling was performed by Diana Pei and Vicky Borders-Hemphill with concurrence from You Zhuo. The OBP labeling assessment will be uploaded as a separate file in Panorama.

VII. Assessment of Common Technical Document- Quality Module 3.2

Critical Quality Attributes	Derived from DS, DP, or Both	Risk	Origin	Control Strategy	Other
Identity					
Identity by peptide mapping	Both	Potency, safety, efficacy	Intrinsic to molecule		(b) (4)

Critical Quality Attributes	Derived from DS, DP, or Both	Risk	Origin	Control Strategy	Other
Identity by Dot Blot	Both	Potency, safety, efficacy	Intrinsic to molecule		(b) (4)
Higher order structure	Both	Potency, safety, efficacy	Intrinsic to molecule		
Biological Activities					
Potency by cell-based bioassay	Both	Potency, safety, efficacy	Intrinsic to molecule, (b) (4) (b) (4) storage and handling		(b) (4)
Antigen binding	Both	Potency, safety, efficacy	Intrinsic to molecule, (b) (4) (b) (4) storage and handling		
FcRn binding	Both	PK, efficacy	Intrinsic to molecule, (b) (4) (b) (4) storage and handling		
General Properties					
Color	Both	Safety and efficacy	Formulation, contamination, and storage	(b) (4)	n/a
Clarity	Both	Safety and efficacy	Formulation, contamination, (b) (4) and storage		n/a
Physical form-Visible particles	DP	Safety, immunogenicity, efficacy	(b) (4) CCS, storage and handling		(b) (4)

Critical Quality Attributes	Derived from DS, DP, or Both	Risk	Origin	Control Strategy	Other
Subvisible particles	DP	Safety, immunogenicity, efficacy	(b) (4) CCS, storage and handling		(b) (4)
pH	Both	Safety and efficacy	Formulation		
Osmolality	Both	Safety and efficacy	Formulation		
Protein concentration	Both	Safety and efficacy	(b) (4) Formulation		
Container Content for Injection	DP	Safety and efficacy	(b) (4)		
Gross Content per vial	DP	Safety and efficacy	(b) (4)		
(b) (4)	Both	Safety and efficacy	Formulation and storage		
Product Variants					
Glycan profile	DS	Potency, immunogenicity, PK, safety, and efficacy	Cell bank and (b) (4)		(b) (4)
Charge variants	Both	Potency,	(b) (4)		

Critical Quality Attributes	Derived from DS, DP, or Both	Risk	Origin	Control Strategy	Other
by iCIEF		immunogenicity, PK, safety, and efficacy	(b) (4) and storage.		(b) (4)
Monomer and Aggregates by SE-UPLC	Both	Potency, immunogenicity, safety, PK and efficacy.	(b) (4) (b) (4) and storage.		
Fragments by (b) (4)	Both	Potency, immunogenicity, safety, PK and efficacy.	(b) (4) (b) (4) and storage.		
Intact IgG and Fragments by (b) (4)	Both	Potency, immunogenicity, safety, PK and efficacy.	(b) (4) (b) (4) and storage.		
Binding impurity (b) (4)	Both	Potency and efficacy	(b) (4)		
Non-binding impurity (b) (4) (b) (4)	Both	Potency, safety and efficacy	(b) (4)		
Process-related Impurities					
Host cell protein (HCP)	DS	Potency, safety, immunog	(b) (4) (b) (4) (b) (4)		(b) (4)

Critical Quality Attributes	Derived from DS, DP, or Both	Risk	Origin	Control Strategy	Other
		enicity, PK and efficacy			(b) (4)
Host cell DNA (HCDNA)	DS	Safety	(b) (4) (b) (4) (b) (4)		
(b) (4)	DS	Potency, safety, immunogenicity, PK and efficacy	(b) (4) (Purification)		
Leachables	Both	Safety	Product-contact materials and CCS		
Contaminants					
Mycoplasma	DS	Safety	Raw materials (b) (4) (b) (4)		(b) (4)
Viral agents	DS	Safety	Raw materials (b) (4) (b) (4)		

VIII. Assessment of Immunogenicity Assays- Module 5.3.1.4

The assessment of immunogenicity assays is provided in this memorandum of review.

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(b) (4)





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Description of Drug Substance and Drug Product

S. Drug Substance

3.2.S.1 General information

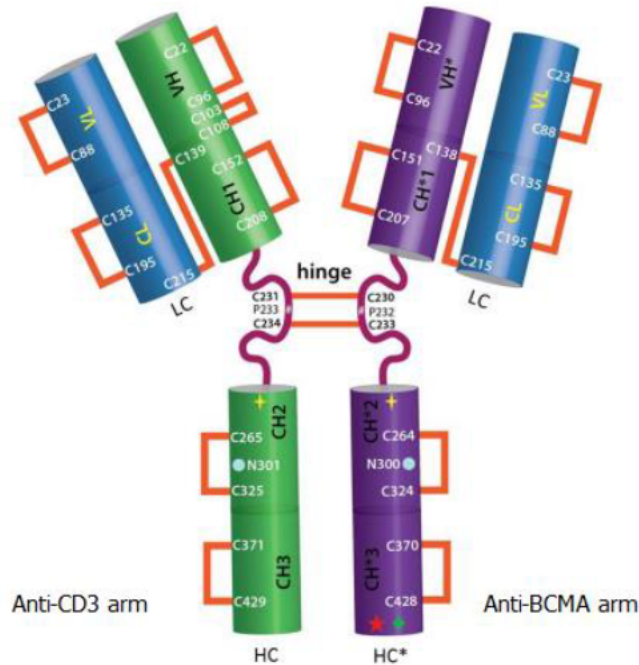
3.2.S.1.2 Structure

Linvoseltamab is an IgG4 based protein containing two identical human kappa light chains (LC), each covalently linked to one of two unique human gamma heavy chains (HC). The complementarity-determining regions (CDRs) within the HC 1 (HC) variable domain are involved in binding to human B-cell maturation antigen (BCMA). The CDRs within the HC 2 (HC*) variable domain are involved in binding to human cluster of differentiation 3 (CD3). The Fc regions were engineered

(b) (4)

(b) (4)

The schematic amino acid sequence indicating, disulfide bond connection, CDRs, glycosylation sites, and engineered mutations on Fc are provided in Section 3.2.S.1.2 [Figure 1](#). The schematic illustration of structure of linvoseltamab shown below is adapted from Section 3.2.S.1.2 [Figure 2](#).



Assessor's comments:

(b) (4)

(b) (4)

3.2.S.1.3 General Properties

Linvoseltamab is a recombinant human bispecific heterotetrameric IgG4-based antibody consisting of a human BCMA binding arm and a CD3 binding arm, which is produced in Chinese hamster ovary (CHO) cells. The proposed mechanism of action of linvoseltamab is to simultaneously bind the BCMA expressing cells and the CD3 expressing T-cells, to enable targeted T-cell mediated lysis of BCMA-presenting cells. The general properties of linvoseltamab are summarized in the following table.

Physical/Chemical Properties	Description
Appearance	Clear to slightly opalescent liquid, colorless to pale yellow
Antibody subclass	Bispecific antibody
Biological target	Human BCMA ($K_D =$ (b) (4) nM) Human CD3 ($K_D =$ (b) (4) nM)
Effector Function	No ADCC or CDC activities in the cell-based ADCC or CDC assays.
Extinction coefficient	(b) (4) $\text{mM}^{-1}\text{cm}^{-1}$ (calculated)
Isoelectric point	(b) (4) measured by iCIEF in the native form
Subunits	Light chain (LC), anti-BCMA heavy chain (HC), anti-CD3 HC
Number of disulfide bonds	17 disulfide bonds including 13 intra-chain disulfide bonds and 4 inter-chain disulfide bonds
Number of cysteines	34

	Free thiol to protein mole ratio: (b) (4)
Molecular weight	(b) (4) Da (Experimentally determined) 145,544 Da (Theoretical)

Refer to Section 3.2.S.3.1 for detailed descriptions and assessment of physicochemical and biological characterizations of linvoseltamab.

3.2.S.2 Manufacture



(b) (4)

(b) (4)



P: Drug Product

3.2.P.1 Description and Composition of the Drug Product

The linvoseltamab drug product (DP) is supplied as a clear to slightly opalescent, and colorless to pale yellow liquid solution, essentially free from visible particulates. The DP is

presented in two strengths, 5 mg/2.5 mL in a 5 mL glass vial and 200 mg/10.0 mL in a 20 mL glass vial. Both strengths are provided in the single-dose (b) (4) clear (b) (4) glass vial sealed with a 20 mm (b) (4) stopper and an aluminum seal cap. The formulation of two presentations only differs in the concentration of linvoseltamab. The components and concentrations of excipients are identical for both presentations. The final composition and formulation for (b) (4) DP is provided below (Adapted from eCTD section 3.2.P.1 Table 1).

Composition	Function	Linvoseltamab DP		
		Concentration	Content (mg)	
			5 mg/2.5 mL per vial	200 mg/10.0 mL per vial
Linvoseltamab	Active ingredient	5 mg: 2 mg/mL 200 mg: 20 mg/mL	5	200
L-Histidine	(b) (4)			
L-Histidine (b) (4) hydrochloride monohydrate				
Polysorbate 80				
Sucrose				
Water for injection				

The viscosity and density were measured for the linvoseltamab DP during the manufacturing process development.

	5 mg vial 2 mg/mL linvoseltamab	20 mg/mL 2 mg/mL linvoseltamab
Viscosity at ambient temperature	1.4 cP	1.6 cP
Density	1.038 g/mL	1.043 g/mL

Assessor's comment: The linvoseltamab DP manufacturing process includes (b) (4) (b) (4) The compositions of excipients for linvoseltamab DS and DP are identical. Therefore, no differences of primary structure, higher order structure, or physical properties are expected between linvoseltamab (b) (4) and DP. The DP specific quality attributes include visible particulates, subvisible particles, gross content per vial, osmolality, sterility, extractable volume, and container closure integrity. An overfill is included for both presentations to ensure deliver the intended volume. The excess volume was experimentally justified to permit withdrawal and administration of the labeled volumes, which was assessed in the section of the DP overfill study.

The dosing regimen for linvoseltamab includes two step-up doses 5 mg and 25 mg, and a full dose of 200 mg. The strength of 5 mg vial for the step-up doses and the 200 mg vial for the full dose are appropriate.

3.2.P.2 Pharmaceutical Development

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You
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Brian
Roelofs

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