CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761310Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	October 28, 2022
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Shadia Zaman, Product Quality Assessor OBP/Division of Biotechnology Review and Research 2
Application:	BLA 761310
Applicant:	ImmunoGen, Inc.
Submission Date:	March 28, 2022
Product:	Elahere (mirvetuximab soravtansine-gynx)
Dosage form(s):	Injection
Strength and Container-Closure:	100 mg/20 mL (5 mg/mL) in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information, medication guide, and carton labeling (submitted on October 20, 2022) and container labels (submitted on October 26, 2022) were assessed and found to be acceptable (see Appendix C) from an OBP 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, medication guide, and carton labeling (submitted on October 20, 2022) and container labels (submitted on October 26, 2022) were assessed and found to be acceptable (see Appendix C) from an OBP Labeling perspective.

APPENDICES

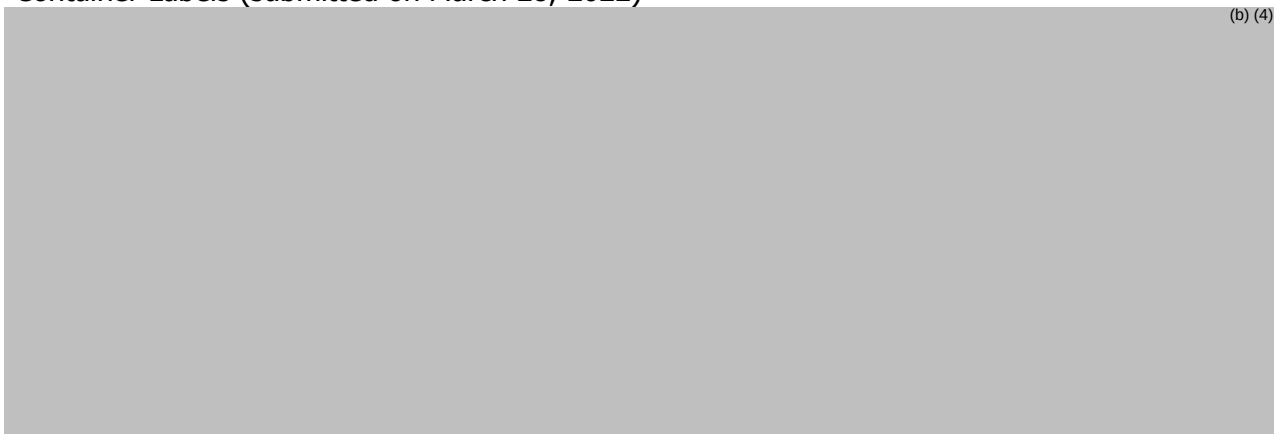
Appendix A: Proposed Labeling

Prescribing Information (submitted on March 28, 2022 \\CDSESUB1\evsprod\bla761310\0001\m1\us\114-label\1141-draft-label\draft-labeling-text-pdf.pdf)

Medication Guide (submitted on March 28, 2022 \\CDSESUB1\evsprod\bla761310\0001\m1\us\114-label\1141-draft-label\medication-guide-pdf.pdf)

Container Labels (submitted on March 28, 2022)

(b) (4)



1 Page of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to the correct dosage form for this product, "Injection" *The Applicant revised as requested*

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

Comment/Recommendation: We acknowledge your proposal to remove the US license number form the container label. We consider this to be important manufacturer information. Consider placing the manufacturer's name and US license number all on one line as follows: "ImmunoGen, Inc. U.S. License: XXXX"

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

The Applicant revised as requested

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

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

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No

	☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

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

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. *Applicant's response: ImmunoGen confirms that the drug product lot number is printed on the aluminum overseal by ink-jet printing machine.*
Acceptable since lot numbers may appear on the side (skirt) surface of the ferrule on vials containing injectable products, but not on the top (circle) surface of the ferrule or cap overseal. The appearance of such statements or features on the skirt surface of the ferrule should not detract from, or interfere with, the cautionary statement on the top surface

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 *Applicant's response: ImmunoGen confirms that sufficient area of the container remains uncovered on its circumference to allow for visual inspection*

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

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

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

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

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

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

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

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

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to	✓ Yes ☐ No

Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	☐ N/A

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

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

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

Comment/Recommendation: Consider revising the storage statement to: "Store vial upright refrigerated at 2°C to 8°C (36 °F to 46 °F) in the original carton to protect from light." *The Applicant revised as requested*

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

Package[6] Labeling Evaluation

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

Comment/Recommendation: Revise to the correct dosage form for this product, "Injection" and consider relocating the dosage form to appear below the proper name
The Applicant revised as requested

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

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

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

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

[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.

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

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

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: Consider revising the storage statement to: "Store vial upright refrigerated at 2°C to 8°C (36 °F to 46 °F) (b) (4) in the original carton to protect from light. Do not freeze or shake." *The Applicant revised acceptably as Store vial upright refrigerated at 2°C to 8°C (36 °F to 46 °F) and in the original carton* (b) (4) (b) (4) *to protect from light. Do not freeze or shake.*

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

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

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

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: List the ingredient amounts and revise to appear in alphabetical order. To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, glacial acetic acid, sodium acetate, sucrose and polysorbate 20.

The established names have been revised to the USP monograph titles. (b) (4) (b) (4) Confirm the calculated amount of sodium acetate (b) (4) (b) (4)

Revise the ingredient names and amounts as follows:

Each mL of solution contains 5 mg of mirvetuximab soravtansine-xxxx, and -glacial acetic acid (0.22 mg), polysorbate 20 (0.1 mg), sodium acetate (b) (4) mg), sucrose (90 mg), and Water for Injection. The pH is approximately 5.0.

Resubmit an updated Description and Composition to section 3.2.P.1 adding a footnote to the table that includes the sodium acetate (b) (4) calculation. Ensure that all inactive ingredients with a USP monograph are provided as such.

Applicant's response: ImmunoGen agrees to updating the names of the excipients to the established names in the USP monograph titles and agrees to the carton label reflecting the list of inactive ingredients to be listed in alphabetical order. ImmunoGen agrees to updating the ingredient names and amounts as proposed. The sodium acetate will be updated to 0.53 mg/mL (b) (4) The updated 3.2.P.1 Description and Composition of the Drug Product is submitted with this sequence to reflect the amounts (b) (4) as requested. The Applicant's revision is acceptable

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

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OBP Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for mirvetuximab soravtansine products (i.e., there is no specific test method described in regulation for mirvetuximab soravtansine 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 Elahere because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No

	☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

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

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

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

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

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

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

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

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

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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

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

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

Comment/Recommendation: The Medication Guide statement shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product

is dispensed and shall state how the Medication Guide is provided. Ensure that the [container label if space permits and/or carton labeling] has the following statement: "ATTENTION: Dispense the [Enclosed or Accompanying] Medication Guide to Each Patient" or "Always Dispense [Enclosed or Accompanying] Medication Guide to Each Patient" *The Applicant revised as requested*

Prescribing Information Evaluation

PRESCRIBING INFORMATION

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

Comment/Recommendation: Revise to the correct dosage form, "Injection" *The Applicant revised as requested*

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

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to the correct dosage form, "Injection" *The Applicant revised as requested*

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the inspection statement "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit." *The Applicant revised as requested* Per OPMA, the microbiology in-use study only supports storage of 24 hours including infusion time (proposal with infusion time is 32 hours). *The Applicant revised* (b) (4) (b) (4) *to read "under refrigeration 2°C to 8°C (36 °F to 46 °F) for no more than 12 hours" and* (b) (4) (b) (4) *to read "After refrigeration, administer diluted infusion within 8 hours (including infusion time)"* *The Applicant revised as requested*

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

Comment/Recommendation: Revise to the correct dosage form for this drug product *The Applicant revised as requested*
The Applicant revised to the corrected color and clarity of solution as clear to slightly opalescent, colorless solution
Revised for concise presentation of information *The Applicant revised as requested*

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, glacial acetic acid, sodium acetate, sucrose and polysorbate 20. The established names have been revised to the USP monograph titles. *The Applicant accepted the revisions*

(b) (4)

(b) (4) Confirm the calculated amount of sodium acetate (b) (4)

(b) (4)

(b) (4) *The Applicant revised the name to sodium acetate and the amount to 0.53 mg*

Revise the ingredient names and amounts accordingly. Resubmit an updated Description and Composition to section 3.2.P.1 adding a footnote to the table that includes the sodium acetate (b) (4) calculation. Ensure that all inactive ingredients with a USP monograph are provided as such.

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html*	✓ Yes ☐ No ☐ N/A

Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	

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

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

Medication Guide Evaluation

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

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

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

Comment/Recommendation: The established names for inactive ingredients in your products are the USP/NF monographs titles, glacial acetic acid, sodium acetate, sucrose and polysorbate 20. The established names have been revised to the USP monograph titles and to appear in alphabetical order *The Applicant revised as requested*

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on October 20, 2022 \\CDSESUB1\EVSPROD\bla761310\0068\m1\us\114-label\1141-draft-label\draft-labeling-text-pdf.pdf)

Medication Guide (submitted on October 20, 2022 \\CDSESUB1\EVSPROD\bla761310\0068\m1\us\114-label\1141-draft-label\medication-guide-pdf.pdf)

1 Page of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 10/28/2022 06:55:31AM
GUID: 50814c7000007a3d59329f660d8ddf02

Shadia Zaman

Digitally signed by Shadia Zaman
Date: 10/28/2022 09:01:03AM
GUID: 583dce940076eea0edb730e401622d6d

First Approval for Indication, Orphan Drug, Fast Track, and Priority Review:

Recommendation: Approval

BLA/NDA Number: 761310
Assessment Number: First Round
Assessment Date: October 3, 2022

Drug Name/Dosage Form	ELAHERE™ [mirvetuximab soravtansine-gynx] Injection
Strength/Potency	100 mg/20 mL in a single-dose vial
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who received one to three prior systemic treatment regimens
Applicant/Sponsor	Immunogen Inc.
Regulatory History	Granted Orphan Drug Designation on July 14, 2015. Granted Fast Track Designation on July 15, 2018. Priority review.

Product Overview:

Mirvetuximab soravtansine is a folate receptor alpha (FRα)-directed antibody-drug conjugate (ADC) consisting of three components: 1) a humanized anti-FRα monoclonal antibody of IgG1 subtype (produced in CHO cells), 2) the small molecule anti-tubulin agent DM4 (a maytansine derivative), and 3) a linker, sulfo-SPDB (1-(2,5-dioxopyrrolidin-1-yl)oxy-1-oxo-4-(pyridin-2-yldisulfanyl)butane-2-sulfonic acid) that covalently attaches DM4 to the mirvetuximab antibody. The ADC preferentially delivers the cytotoxic anti-mitotic agent, DM4, to FRα positive cells. FRα is highly expressed on the cell surface of several solid tumors including epithelial ovarian cancer cells. The payload, DM4, inhibits tubulin polymerization and microtubule assembly, resulting in cell cycle arrest and apoptosis of the target cells. The mirvetuximab soravtansine manufacturing process was designed to deliver an average of 3.4 DM4 molecules per antibody molecule [maytansinoid-to-antibody ratio (MAR) = 3.4].

ELAHERE (mirvetuximab soravtansine-gynx, referred to as mirvetuximab soravtansine in the rest of the review) is provided as a sterile, preservative-free, clear to slightly opalescent, colorless solution containing 100 mg/20 mL of mirvetuximab soravtansine in single-dose vials. It is intended for intravenous infusion after dilution in 5% Dextrose Injection, USP. Each mL of solution contains 5 mg of mirvetuximab soravtansine, and glacial acetic acid (0.22 mg), polysorbate 20 (0.1 mg), sodium acetate (0.53 mg), sucrose (90 mg), and Water for Injection. The pH is approximately 5.0.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance/Drug Product	Arulvathani Arudchandran	CDER/OPQ/OBP/DBRRII
Small Molecule	Rajan Pragani	CDER/OPQ/ONDP
Immunogenicity	Arulvathani Arudchandran	CDER/OPQ/OBP/DBRRII
Labeling	Vicky Borders-Hemphill	CDER/OPQ/OBP
Facility	Richard Ledwidge	CDER/OPQ/OPMA/DBM/BMB2
Microbiology	Reyes Candau-Chacon	CDER/OPQ/OPMA/DBM/BMB2
Team Leads	Shadia Zaman (Product quality) Paresma Patel (Small molecule) Michael Shanks (Facility) Virginia Carroll (Microbiology)	CDER/OPQ/OBP/DBRRII CDER/OPQ/ONDP CDER/OPQ/OPMA/DBM/BMB2 CDER/OPQ/OPMA/DBM/BMB2

Application Team Lead	Shadia Zaman	CDER/OPQ/OBP/DBRRII
Application Tertiary Reviewer	Patrick Lynch	CDER/OPQ/OBP/DBRRII
Regulatory Business Project Manager	Andrew Shiber	CDER/OPQ/OPRO

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Alice Lee	
Cross-disciplinary Team Lead	Gwynn Ison	CDER/OND/OOD/DO1
Medical Officer (Efficacy)	Mirat Shah	CDER/OND/OOD/DO1
Medical Officer (Safety)	Asma Dilawari	CDER/OND/OOD/DO1
Pharmacology/Toxicology	Wimolnut Manheng/ Tiffany Ricks	CDER/OND/OOD/DHO
Clinical Pharmacology	Ankit Shah/ Salaheldin Hamed	CDER/OTS/OCP/DCPI
Statistics	Haley Gittleman/ Mallorie Fiero	CDER/OTS/OB/DB

1. Names:

a. Proprietary Name: ELAHERE™
b. Trade Name: ELAHERE™
c. Non-Proprietary Name/USAN: Mirvetuximab soravtansine-gynx, BC-78
d. CAS Name: 1453084-37-1
e. Common Name: N/A
f. INN Name: Mirvetuximab soravtansine
g. Compendial Name: None
h. OBP systematic name: CONJ: MAB HUMANIZED (IGG1) ANTI P15328 (FOLR1_HUMAN); MAYTANSINOID DM4 [IMGN853]

Submissions Assessed:

Submission(s) Assessed	Document Date
BLA 761310.0001- Initial submission	March 28, 2022
BLA 761310.0007- OPMA IR#1 response (Shipping of M9346A)	May 11, 2022
BLA 761310.0009- OBP IR response #1	May 18, 2022
BLA 761310.0012- OBP IR response #2	June 2, 2022
BLA 761310.0013- Update to Sections 3.2.S.2.2-M9346A, 3.2.R- OBP request	June 6, 2022
BLA 761310.0015- Stability update, OBP IR#1 – Q6	June 13, 2022
BLA 761310.0017- OBP IR#3 response	June 16, 2022
BLA 761310.0020- OBP IR#3 response	July 5, 2022
BLA 761310.0022- OBP IR#4 response	July 13, 2022
BLA 761310.0024- OBP IR#5 response	July 21, 2022
BLA 761310.0025- OPMA IR#2 response	July 22, 2022
BLA 761310.0026- ONDP IR response	July 26, 2022
BLA 761156.0031- OBP IR#6 response	August 8, 2022
BLA 761310.00333 (follow up to OBP IRs #5, 6)	August 12, 2022
BLA 761310.0034- OBP IR#7 response	August 15, 2022

BLA 761310.0036- OBP IR#8 response	August 22, 2022
BLA761310.0037- Shipping protocol, follow up to OBP IR#6 response	August 23, 2022
BLA 761310.0039- OPMA IR#3 response	August 30, 2022
BLA 761310.0041- OPMA Follow-up to General Advice Letter sent on August 5, 2022	September 1, 2022
BLA 761310.0042- OBP IR#9 response	September 6, 2022
BLA 761310.0043- OPMA Follow-up to OPMA IR#3 response	September 8, 2022
BLA 761310.0045- OBP IR#10 response and OPMA Follow-up to General Advice Letter sent on August 5, 2022	September 14, 2022
BLA 761310.0046- Follow-up to OPMA IR#2 response	September 15, 2022
BLA 761310.0047- OPMA IR#4 response	September 16, 2022
BLA 761310.0052- OPMA IR#5 response	September 20, 2022
BLA 761310.0053- OPMA IR#6 and OPMA Follow-up to General Advice Letter sent on September 19, 2022 response	September 22, 2022
BLA761310.0055- OBP IR#11 response	September 23, 2022
BLA 761310.0057- Follow-up to OPMA IR#5 response	September 28, 2022
BLA 761310.0060- Follow-up to OPMA IR#5 response	October 4, 2022
BLA 761310.0061- OPMA IR#6 response	October 7, 2022
BLA 761310.0062- Follow-up to OPMA IR#5 response	October 7, 2022
BLA 761310.0064- OPMA IR#7 response	October 11, 2022

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

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Assessment Completed	Comments
(b) (4)	V	(b) (4)	Contract manufacturing facility information	3	Adequate	N/A	N/A

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows: 2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be assessed.

B. Other documents:

Document	Application Number	Description
IND	111915	Investigation for the use of mirvetuximab soravtansine for the treatment of adult patients with FOLR1 expressing solid tumors, initially submitted on March 16, 2012.

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion:

A claim for a categorical exclusion is made under 21 CFR 25.31 (b). This application is for a marketing approval of a biologic product, mirvetuximab, an antibody that is conjugated to a cytotoxic small molecule, maytansinoid (DM4). DM4 is the active pharmaceutical ingredient (API) of the antibody drug conjugate (ADC). ImmunoGen's calculations show that the expected introduction concentration for DM4 will be (b) (4) part per billion (ppb). ImmunoGen Inc. claimed for a categorical exclusion from the requirement to prepare an environmental assessment (EA) based on the estimated concentration of API, less than 1 ppb of the active moiety (DM4) will be introduced into the aquatic environment. In addition, the Sponsor claims that no extraordinary circumstances exist per 21 CFR 25.15(d) that would warrant the preparation of an environmental assessment.

Therefore, the claim of categorical exemption for ELAHERE is accepted.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Biotechnology Products, OPQ, CDER, recommends approval of STN 761310 for ELAHERE (mirvetuximab soravtansine) manufactured by ImmunoGen, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of ELAHERE 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 conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance and Drug Product: (b) (4) (FEI: (b) (4))
  - M9346A Antibody Intermediate: (b) (4) (b) (4) (FEI: (b) (4))
  - DM4 Payload: (b) (4) (FEI: (b) (4))
  - Sulfo-SPDB linker: (b) (4) (FEI: (b) (4))
- Fill size and dosage form: 100 mg/20 mL solution in single-dose vial
- Dating period:
  - Drug Product: 60 months: 5±3 °C
  - Drug Substance: (b) (4) months: (b) (4) °C
  - M9346A Antibody Intermediate: (b) (4) months: (b) (4) °C
  - For packaged products: Not packaged
  - Stability Option:
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
- Exempt from lot release:
  - Yes, ELAHERE is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

The assessment of manufacturing information provided in the application and in the cross-referenced drug master file (DMF) has concluded that the methodologies and processes used

for the M9346A antibody intermediate, DM4 payload, sulfo-SPDB linker, drug substance, and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The antibody intermediate and drug substance manufacturing processes are robust for removal and control of adventitious agents. No approvability issues were identified from a sterility assurance or microbiology product quality perspective.

The mirvetuximab antibody intermediate will be manufactured at (b) (4) (b) (4) (FEI: (b) (4)), the DM4 payload will be manufactured at (b) (4) (b) (4) (FEI: (b) (4)), the sulfo-SPDB linker will be manufactured at (b) (4) (b) (4) (FEI: (b) (4)), mirvetuximab soravtansine drug substance (DS) will be manufactured at (b) (4) (FEI: (b) (4)), and the ELAHERE drug product (DP) at (b) (4) (FEI: (b) (4)). All facilities for manufacturing and quality control testing were found acceptable for the proposed operations.

The immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) and neutralizing antibodies (NAb) in presence of mirvetuximab soravtansine at plasma concentrations.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

1. To provide results for the stability indicating product quality attributes of the IMGN853 DP shipped during the summer and winter months from the (b) (4) manufacturing site to the end-users. Submit the final study report containing data for the product quality attributes and shipping container temperatures (internal, external) from the drug product shipping studies performed per the performance qualification protocols to BLA 761310 to qualify the commercial shipping process of mirvetuximab soravtansine DP. Final report will be submitted by December 2023.
2. To validate a gravimetric method to test the mirvetuximab soravtansine drug product (DP) gross content/vial. Submit the final study report containing the description of the method and the results to support that the gravimetric method is suitable to test the DP gross content/vial. Final report will be submitted by June 2023
3. To repeat the endotoxin method verification for in-process samples of drug substance (DS) intermediate with one additional batch of product verifying the lysate sensitivity in quadruplicates as per USP <85> and update Section S.2.4 of the DS intermediate. The final report will be submitted by May 31, 2023.
4. To conduct a study to identify where (b) (4) occurs in the DS manufacturing process and to implement an additional (b) (4) specification (b) (4) (b) (4) Final report will be submitted by June 30, 2023.
5. To develop a method capable of reliably detecting endotoxin levels for release testing of DS and DP, to perform method qualification with three batches of product and to implement the new endotoxin detection method. Final report will be submitted by December 31, 2023.
6. To provide the shipping validation report of the drug substance intermediate (b) (4) (b) (4) Final report will be submitted by December 31, 2024.

7. To submit (b) (4) sterilization validation report demonstrating sterility assurance (b) (4) Final report will be submitted by June 30, 2023.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 is a summary of product-related critical quality attributes (CQA), intrinsic to the molecule, that are relevant to the antibody intermediate (AI), drug substance (DS), and drug product (DP). The table includes the identification of the various attributes along with their risk management.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Quality Attribute	Risk	Origin	Control Strategy
Identity	Identity	Efficacy, safety	Intrinsic to the molecule	(b) (4)
Bioactivity/Potency	Potency by direct binding	Bioactivity, efficacy, safety	Intrinsic to the molecule	
	Specific cytotoxicity by cell-based assay	Impacted by (b) (4) (b) (4) Bioactivity, efficacy, safety	Intrinsic to the molecule	
Size-related variants	HMW species	Impacted by (b) (b) (4) PK, safety (immunogenicity)	Manufacturing process, storage	
	LMW species/ fragments	Impacted by (b) (4) (b) (4) Safety (immunogenicity)	Manufacturing process, storage	
Charge-related variants	Acidic and basic variants	No impact to biological activity of mirvetuximab soravtansine (FRα binding, specific cytotoxicity). Potential impact to safety.	Manufacturing process, storage	

				(b) (4)
Oxidation-related variants	Met 253 and Met 429 oxidation in the conserved Fc region of the antibody heavy chain.	No significant impact on FRα binding and specific cytotoxicity. No impact on attributes characterized by SEC (HMW and LMW), NR-CGE (fragments and non-dissociable species), R-CGE (LMW and non-reduced species), FM, and MAR. Decreased FcRn binding. Potential impact to PK.		
Conjugation-Related Variants	Maytansinoid distribution profile (MDP) D0 – D7	Efficacy and safety	DS manufacturing process (b) (4)	
	Maytansinoid to antibody ratio (MAR)	Impacted by (b) (4) (b) (4) Efficacy and safety	DS manufacturing process (b) (4)	
	Unconjugated MAb (UMAb) (D0)	(b) (4) Efficacy and safety	DS manufacturing process (b) (4)	
	Total DM4 concentration	Impacted by (b) (4) (b) (4)	(b) (4) (b) (4)	

		Efficacy and safety	manufacturing process (b) (4) (b) (4)	(b) (4)
Free maytansinoids	Total maytansinoids	(b) (4) Safety	DS manufacturing process (b) (4)	
	Maysine	Safety	DS manufacturing process (b) (4)	
	DM4	Safety	DS manufacturing process (b) (4)	
	DM4-sulfo-TBA	Safety	DS manufacturing process (b) (4)	
	Individual unspecified species	Safety	DS manufacturing process (b) (4)	

B. Antibody Intermediate [mirvetuximab] Quality Summary

Table 2 provides a summary of the identification, risk, and lifecycle knowledge management for the antibody intermediate-specific CQAs.

Table 2: Antibody Intermediate CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	CQA	Risk	Origin	Control Strategy
(b) (4)				

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(b) (4)

- Description: Mirvetuximab antibody intermediate is (b) (4)
  (b) (4)
  (b) (4)
- Mechanism of Action (MoA): The primary MoA of mirvetuximab antibody intermediate is
  (b) (4)
- Potency Assay: (b) (4)
  (b) (4)
- Reference Materials: (b) (4)
  (b) (4)

(b) (4)

- Critical starting materials or intermediates: Mirvetuximab is produced by (b) (4)
(b) (4)
- Manufacturing process summary: Mirvetuximab antibody intermediate is produced in (b) (4)
- Container closure: Mirvetuximab antibody intermediate is stored (b) (4)
(b) (4)
- Dating period and storage conditions: (b) (4) months at (b) (4) °C.

C. Drug-linker Intermediate Quality Summary

The drug-linker is composed of a DM4 payload intermediate and a sulfo-SPDB linker intermediate. The DM4 payload is conjugated to the sulfo-SPDB to form an *in situ* drug-linker intermediate. This molecule is then conjugated to the M9346A antibody intermediate to product IMGN853 drug substance.

Data supporting appropriate control of DM4 payload and sulfo-SPDB linker stability and controls/limits on small molecule impurities, residual solvents, residual metals, and conjugation impurities are

discussed in the appropriate manufacturing sections in the BLA and found acceptable by the ONDP assessor (review uploaded in Panorama on September 8, 2022 by Rajan Pragani).

D. Drug Substance [mirvetuximab soravtansine] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 3: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Quality Attribute	Risk	Origin	Control Strategy
Process-related impurities - (b) (4) (b) (4)	Total maytansinoids	Potential impact to safety	DS manufacturing process (b) (4)	(b) (4)
	Maysine			
	DM4			
	DM4-sulfo-TBA			
	Individual unspecified species			
Residual solvent	Residual DMA	Potential impact to safety	DS manufacturing process (b) (4)	
Process-related impurities	Leachables	Potential impact to safety (immunogenicity)	Raw materials, product-contacting equipment and materials	
Microbial control	Bioburden	Safety, purity, and efficacy due to degradation or modification of the product by microbial contamination	Raw materials, manufacturing process	
	Endotoxin	Safety and purity	Raw materials, manufacturing process	

Content composition and strength	Protein concentration	Efficacy	Manufacturing process (formulation)	(b) (4)
	Color	Safety	Formulation	
	Clarity	Safety	Formulation	
	pH	Stability, safety	Formulation	
	Osmolality	Bioactivity	Formulation	

- Description: Mirvetuximab soravtansine consists of a humanized IgG1 anti-FRα mAb (mirvetuximab AI) conjugated via a cleavable sulfo-SPDB (glycosylphosphatidylinositol) linker to a cytotoxic anti-mitotic agent, maytansinoid (DM4). The DM4 and sulfo-SPDB molecules are linked through a disulfide bond. The linker-drug is conjugated via an amide bond with epsilon amino groups on lysine residues of the antibody. The amide bond is formed with the NHS ester group on sulfo-SPDB.
- Mechanism of Action (MoA): Upon binding to FRα, mirvetuximab soravtansine undergoes receptor-mediated internalization and subsequent degradation in the lysosome. This releases DM4-containing cytotoxic catabolites (primarily S-methyl-DM4). These catabolites bind to tubulin and disrupt microtubule networks in the cell, resulting in cell cycle arrest and apoptosis. The catabolites may also diffuse across the cell membrane and kill the neighboring cells (bystander killing), enabling the conjugate to be active against tumors with heterogeneous expression of FRα.
- Potency Assay: Two potency methods relevant to the MoA are included in the commercial control strategy:
  - Potency by direct binding: ELISA that measure the ability of conjugated antibody to bind FRα
  - Potency by specific cytotoxicity: Cell-based assay that measures the ability of conjugated antibody to kill FRα expressing cells.
- Reference Materials: (b) (4) (b) (4)
- Critical starting materials or intermediates:
  - Antibody Intermediate: Mirvetuximab AI is manufactured and stored as described above.
  - DM4 Intermediate: DM4 is manufactured and stored as described in the BLA.
  - Sulfo-SPDB Intermediate: Sulfo-SPDB is manufactured and stored as described in the BLA.
- Manufacturing process summary: (b) (4) (b) (4)

(b) (4)

- Container closure: (b) (4)
- Dating period and storage conditions: (b) (4) months at (b) (4) °C.

E. Drug Product [ELAHERE] Quality Summary:

Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 4: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Quality Attribute	Risk	Origin	Control Strategy (b) (4)	Other
Particles	Visible particulates	Safety, immunogenicity, and stability	Manufacturing process, storage		
	Subvisible particulate matter	Safety, immunogenicity, and stability	Manufacturing process, storage		
Composition, strength	Protein concentration	Efficacy, stability	Manufacturing process		
	pH	Stability	Manufacturing process		
	Osmolality	Stability	Manufacturing process		
	Polysorbate 20 concentration	Stability	Manufacturing process		
	Extractable volume	Efficacy, stability	Manufacturing process		
	Gross content	Efficacy	Manufacturing process		
Physical characteristics	Color	Stability	Manufacturing process, storage, contamination		
	Clarity	Stability	Manufacturing process, storage, contamination		
Microbial control and sterility assurance	Sterility (Contaminant)	Safety, purity, and efficacy	Manufacturing process, failure of the container closure integrity		

				(b) (4)	
	Pyrogens (Contaminant)	Safety, purity	Raw materials, manufacturing process		(b) (4)
	Container closure integrity (Sterility assurance)	Safety (Sterility assurance)	Breach during manufacture or storage		
Elemental impurities	(b) (4)	Safety and purity	(b) (4) manufacturing process.		

- Potency and Strength: 100 mg/20 mL of mirvetuximab soravtansine in single-dose vial.
- Summary of Product Design: For intravenous infusion after dilution with 5% dextrose
- List of Excipients: (b) (4) mM acetate (b) (4)% (w/v) sucrose, (b) (4) % (w/v) polysorbate 20, pH 5.0
- Reference Materials: Same as mirvetuximab soravtansine drug substance
- Manufacturing process summary: Mirvetuximab soravtansine drug product is a liquid drug product in a 20 mL vial designed to deliver 100 mg drug product per vial. The target fill volume is (b) (4) mL/vial. DP filling operation is conducted (b) (4)
(b) (4)

(b) (4)

(b) (4) Container closure integrity testing using a validated method is included in the stability program.

- Container closure: (b) (4) 20 mL (b) (4) clear (b) (4) glass vial with a 20 mm grey (b) (4) rubber stopper. Aluminum seal with a royal blue (b) (4) flip cap.
- Dating period and storage conditions: 60 months at 5±3°C

F. Novel Approaches/Precedents: None

G. Any Special Product Quality Labeling Recommendations:

1. Store vials upright at 2°C to 8°C.
2. Protect from light.
3. Do not freeze or shake.
4. ELAHERE must be diluted prior to administration with 5% Dextrose Injection, USP to a final concentration of 1 mg/mL to 2 mg/mL.
5. ELAHERE is incompatible with 0.9% Sodium Chloride Injection. ELAHERE must not be mixed with any other drugs or intravenous fluids.
6. If the diluted drug solution is not used immediately, store solution either at ambient temperature (18°C to 25°C) for no more than 8 hours (including infusion time), or under refrigeration at 2°C to 8°C for no more than 12 hours. After refrigeration, administer diluted infusion solutions within 8 hours (including infusion time).
7. Do not freeze prepared infusion solution.

H. Establishment Information:

Overall Recommendation: **Approval**					
ANTIBODY INTERMEDIATE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
• Quality control of raw materials • Oversite of raw material storage sites • Manufacturing of M9346A antibody • In-process control testing • Release Testing (except transmission electron microscopy) • Stability Testing	(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Adequate based on history. OPMA and OBP concurred with an Inspection Waiver.	N/A	Approval
• Storage of master cell bank		FEI: (b) (4) DUNS: 1 (b) (4)	Adequate based on history.	N/A	Approval

	(b) (4)				
• Storage of master cell bank		DUNS: (b) (4)		N/A	No Evaluation Necessary
• Manufacturing of cell bank		DUNS: (b) (4)		N/A	No Evaluation Necessary
• Release Testing (Transmission Electron Microscopy)		FEI: (b) (4) DUNS: (b) (4)	Adequate based on history	N/A	Approval
• Storage of M9346A antibody		FEI: (b) (4) DUNS: (b) (4)	Adequate based on history	N/A	Approval
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
• Quality control and storage of raw materials • Manufacturing of drug substance • In-process control testing • Release Testing (except for Rabbit Pyrogen testing) • Stability Testing • Storage of DS	(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Adequate based on history. OPMA and OBP concurred with an Inspection Waiver.	N/A	Approval
• Release Testing for Rabbit Pyrogen testing		FEI: (b) (4) DUNS: (b) (4)	Adequate based on history	N/A	Approval
DRUG PRODUCT					

Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
• Manufacturing of drug product • Release Testing (except for Rabbit Pyrogen testing and Elemental Impurities) • Stability Testing (except for Rabbit Pyrogen testing)	(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Adequate based on history. OPMA and OBP concurred with an Inspection Waiver.	N/A	Approval
• Release Testing (Rabbit Pyrogen testing only) • Stability Testing (Rabbit Pyrogen testing only)		FEI: (b) (4) DUNS: (b) (4)	Adequate based on history	N/A	Approval
• Release Testing (Elemental Impurities only)		FEI: (b) (4) DUNS: (b) (4)	Adequate based on history	N/A	Approval
• Labeling and packaging • Storage		FEI: (b) (4) DUNS: (b) (4)	Adequate based on history	N/A	Approval

I. Facilities:

- (b) (4) (FEI: (b) (4)) (b) (4) is responsible for manufacture of the mirvetuximab antibody intermediate. A pre-license inspection was waived by OBP/OPMA based on previous inspectional history of the manufacturing area and experience with the equipment and manufacturing process with **Final facility recommendation: Approval.**

- (b) (4) (FEI: (b) (4)) (b) (4) is responsible for the manufacture of the mirvetuximab soravtansine bulk drug substance and drug product. A pre-license inspection was waived by OBP/OPMA based on previous inspectional history of the manufacturing area and experience with the equipment and manufacturing process with **Final facility recommendation: Approval**

J. Lifecycle Knowledge Management:

1. Antibody Intermediate:

i. Protocols approved:

Protocol	BLA section/reporting category	Regulatory Reporting
Comparability protocol for new product introductions (b) (4) (b) (4)	Section 3.2.R	Annual Report
Post-approval stability protocol	Section 3.2.S.7.2 (M9346A Antibody)	Annual Report
(b) (4) life-time concurrent validation protocols (b) (4)	Section 3.2.S.2.5 (M9346A Antibody)	Annual Report
(b) (4) lifetime concurrent validation protocol	Section 3.2.S.2.5 (M9346A Antibody)	Annual Report
Qualification protocol for a new working reference material -M9346A antibody	Section 3.2.S.5 (M9346A Antibody)	Annual Report

ii. Outstanding assessment issues/residual risk: None

iii. Future inspection points to consider: None identified.

2. Drug Substance:

i. Protocols approved:

Protocol	BLA section/reporting category	Regulatory Reporting
Comparability protocol for new product introductions (b) (4) (b) (4)	Section 3.2.R	Annual Report
Post-approval stability protocol	Section 3.2.S.7.2 (DS)	Annual Report
Qualification protocol for a new working reference material - DS	Section 3.2.S.5 (DS)	Not Indicated

ii. Outstanding assessment issues/residual risk: None

iii. Future inspection points to consider: None identified.

3. Drug Product

i. Protocols approved:

Protocol	BLA section/reporting category	Regulatory Reporting
Post-approval stability protocol	Section 3.2.P.8.2 (DP)	Annual Report

ii. Outstanding assessment issues/residual risk: None

iii. Future inspection points to consider: None identified.

Shadia Zaman

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Patrick Lynch

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