

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761171Orig1s000

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:	November 16, 2020
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Ian McWilliams, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 2
Application:	BLA 761171
Applicant:	Y-mAbs Therapeutics, Inc.
Submission Date:	March 31, 2020
Product:	Danyelza (naxitamab-gqgk)
Dosage form(s):	Injection
Strength and Container-Closure:	40 mg/10 mL (4 mg/mL)
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information and patient information labeling (submitted on November 9, 2020) and container labels and carton labeling (submitted on October 23, 2020) are acceptable 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 and patient information labeling (submitted on November 9, 2020) and container labels and carton labeling (submitted on October 23, 2020) are acceptable from an OBP labeling perspective (see Appendix C).

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted on March 31, 2020

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Container Labels (submitted on March 31, 2020)

(b) (4)

Carton Labeling (submitted on March 31, 2020)

(b) (4)



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(h)(2)(i)(1)(i)	☒ 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

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
<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 label⁵)</i>	☒ Yes ☐ No ☐ N/A

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

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."

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, 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</i>	☒ Yes ☐ No ☐ N/A

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

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: 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</i>	☒ Yes ☐ No ☐ N/A

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

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: 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</i>	☒ 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
<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.
Applicant's response: Y-mAbs confirms that there is no text on the ferrule and cap overseal of the vials.

Visual inspection	Acceptable
Regulation: 21 CFR 610.60(e)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located
Applicant's response: Y-mAbs confirms that there is sufficient area of the container that remains uncovered to allow for visual inspection when the label is affixed to the container.

The visual area of inspection is located in the gap where the area of the container remains uncovered for its full length.

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

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
<i>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</i>	☐ Yes ☐ No ☒ N/A

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) USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to the appropriate package-type term for this product is "single-dose".
The Applicant revised as requested

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
<i>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</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Ensure that a linear barcode appears on the container label
The Applicant revised as requested

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
<i>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</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ 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

Comment/Recommendation: Consider revising from (b) (4) to read "Dosage: See Prescribing Information"
The Applicant revised as requested using "recommended dosage" per DMEPA review

Inactive ingredients (container label)	Acceptable
Regulation: 21 CFR 201.100	☐ 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

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

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

Package⁶ Labeling Evaluation

<u>Proper name (package labeling)</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	☒ 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

<u>Manufacturer name, address, and license number (package labeling)</u>	<u>Acceptable</u>
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

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

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

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

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: Revise to (b) (4)

The Applicant revised to the DMEPA requested phrase "Store refrigerated at 2°C to 8°C (36°F to 46°F). Keep vial in outer carton to protect from light."

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
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ 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
<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: Revise the ingredient statement so that the inactive ingredients appear in alphabetical order as follows: "Each single-dose vial contains 40 mg of naxitamab-gqgk in 10 mL of solution. Each mL of solution contains 4 mg of naxitamab-gqgk, and citric acid anhydrous (0.71 mg), poloxamer 188 (1.5 mg), sodium chloride (7.01 mg), sodium citrate (6.3 mg), and Water for Injection, USP. The pH is approximately 5.7.
The Applicant revised as requested

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

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

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: 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</i>	☒ 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
<i>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)</i>	☒ 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
<i>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</i> <i>USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to the appropriate package-type term for this product is "single-dose". *The Applicant revised as requested*

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
<i>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</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ 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

Comment/Recommendation: Consider revising from [REDACTED] (b) (4) to read
 "Dosage: See Prescribing Information"
The Applicant revised to DMEPA's requested Recommended Dosage: See Prescribing Information. Acceptable

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

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

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

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: Revised to the appropriate package type term for your product, single-dose vial.
Applicant revised as requested

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 drug; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes); confirm product's incompatibilities, and 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</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: the storage requirement for the supplied product are provided in section 16 (How supplied/storage and handling) and deleted from this section since it is not required to appear here.
Applicant revised as requested

The infusion solutions were revised to USP nomenclature (5% Albumin (Human), USP and 0.9% Sodium Chloride Injection, USP)
Applicant revised as requested

FDA does not have sufficient information to support the proposed storage duration and will limit the storage time to 4 hours if you do not provide this information prior to the action date for this application: "If not used immediately, store the diluted DANYELZA infusion solution at

room temperature (15°C to 25°C [59°F to 77°F]) for up to 4 hours or refrigerate (2 to 8°C [36°F to 46°F]) for up to 24 hours. Once removed from refrigeration, initiate infusion within 4 hours"

The Applicant revised to "If not used immediately, store the diluted DANYELZA infusion solution at room temperature (15°C to 25°C [59°F to 77°F]) for up to 8 hours or refrigerate (2 to 8°C [36°F to 46°F]) for up to 24 hours. Once removed from refrigeration, initiate infusion within 8 hours"

OPMA determined acceptability for the 8 hours storage condition

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

Comment/Recommendation: The dosage form has been added
Applicant revised as requested
 The total amount/total mL strength presentation has been added
Applicant revised as requested
 Confirm the complete information regarding the clarity and color of the drug product
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
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: The (b) (4) has been deleted from this first paragraph since it discusses the drug substance

Applicant revised as requested
 The pharmacological class was added per 21 CFR 201.57(c)(12)
Applicant revised as requested
 the cell line was added.
Applicant revised as requested
 request that you add the molecular weight of the drug substance
Applicant revised as requested
 the dosage form has been added
Applicant revised as requested
 Confirm and/or provide the complete information regarding the clarity and color of the drug product
Applicant revised as requested

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

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

Comment/Recommendation: The dosage form has been added
Applicant revised as requested
 Confirm and/or provide the complete information regarding the clarity and color of the drug product
Applicant revised as requested
 the in-use storage conditions have been deleted since it is already provided section 2
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: a placeholder for the U.S. license number has been provided
Applicant revised as requested

Patient Information Labeling Evaluation

PATIENT INFORMATION LABELING	
TITLE (NAMES AND DOSAGE FORM)	Acceptable
<i>Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).</i>	☒ Yes ☐ No ☐ N/A

PATIENT INFORMATION LABELING	
STORAGE AND HANDLING	Acceptable
<i>Recommended labeling practices for Patient Labeling: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)</i>	☐ Yes ☐ No ☒ N/A

PATIENT INFORMATION LABELING	
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

PATIENT INFORMATION LABELING	
MANUFACTURER INFORMATION	Acceptable
21 CFR 201.1, 19 CFR 134.11	☒ 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

Medication Guide Evaluation (N/A)
Instructions for Use Evaluation (N/A)

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on November 9, 2020

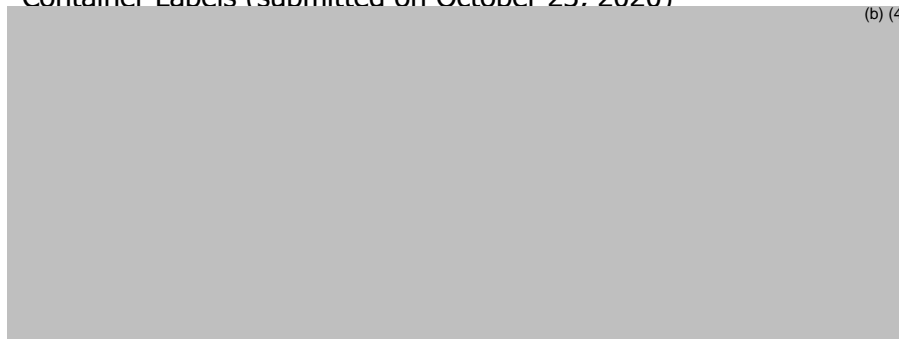
<\\CDSESUB1\evsprod\bla761171\0083\m1\us\114-labeling\draft\labeling\draft-labeling-text-word-track-changes-09-november-2020.docx>)

Patient Information Labeling (submitted November 9, 2020

<\\CDSESUB1\evsprod\bla761171\0083\m1\us\114-labeling\draft\labeling\draft-patient-package-insert-word-track-changes-09-november.docx>)

Container Labels (submitted on October 23, 2020)

(b) (4)





Vicky
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 11/17/2020 02:21:55PM
GUID: 50814c7000007a3d59329f660d8ddf02



Ian
McWilliams

Digitally signed by Ian McWilliams
Date: 11/16/2020 01:39:18PM
GUID: 5d8bbaa900b13f329712ebc94d4e8daa

First Approval for Indication

Recommendation: BLA Approval

BLA Number: 761171
Original Review Date: October 7th, 2020
Date of Review Amendment: November 13th, 2020

Drug Name/Dosage Form	Danyelza (naxitamab-xxxx) for intravenous use
Strength/Potency	4.0 mg/mL (40 mg/10 mL) single dose vial
Route of Administration	Intravenous use
Rx/OTC dispensed	Rx
Indication	Treatment of refractory or relapsed high-risk neuroblastoma in bone (b) (4) or bone marrow in combination with GM-CSF
Applicant/Sponsor	Y-mAbs Therapeutics, Inc.

Product Overview

Danyelza (naxitamab-xxxx) is a recombinant, humanized IgG1κ monoclonal antibody with an approximate molecular weight of 144 kilodaltons that is produced using Chinese Hamster Ovary (CHO) cells. Naxitamab binds to the disialoganglioside GD2 (GD2), which is preferentially expressed on tumor cells of neuroectodermal origin. Upon binding, naxitamab induces cell killing by Fc-mediated immune responses including antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Naxitamab drug product (DP) is a sterile solution for infusion. Each vial of naxitamab DP contains 4.0 mg/mL of naxitamab in (b) (4) consisting of 62.6 mg sodium citrate, 7.1 mg anhydrous citric acid, 70.1 mg sodium chloride, 15 mg Poloxamer 188 (b) (4) and water for injection. Each DP vial contains a total volume of (b) (4). The treatment regimen is 3 mg/kg/day, infused three times per cycle on days 1, 3 and 5 (b) (4). GM-CSF is administered on the 5 days preceding the first infusion of naxitamab-xxxx at a dose of 250 µg/m²/day.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance (DS)	Ian McWilliams	OPQ/OBP/DBRR11
DP	Ian McWilliams	OPQ/OBP/DBRR11
Immunogenicity	Ian McWilliams	OPQ/OBP/DBRR11
Labeling	Vicky Borders Hemphill Ian McWilliams	OPQ/OBP OPQ/OBP/DBRR11
DS Micro and Facilities	Viviana Matta	OPQ/OPMA/DBM2
DP Micro and Facilities	Yun Wu	OPQ/OPMA/DBM2
RBPM	Anika Lalmansingh	OPQ/OPRO
Team Lead	Brian Roelofs Maxwell Van Tassell (DS Micro) Virginia Carroll (DP Micro) Zhihao (Peter) Qiu (Facilities)	OPQ/OBP/DBRR11 OPQ/OPMA/DBM1 OPQ/OPMA/DBM2 OPQ/OPMA/DBM
Application Technical Lead	Brian Roelofs	OPQ/OBP/DBRR11

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Rebecca Cohen	OND/ORO/DROOD
Cross-disciplinary Team Lead	Amy Barone	OND/OOD/DOII
Medical Officer	Diana Bradford	OND/OOD/DOII
Pharm/Tox	Stephanie Aungst/Whitney Helms	OND/OOD/DHOT
Clinical Pharmacology	Catharine Bulik/Hong Zhao	OTS/OCP/DCPI
Statistics	Xiaoxue Li/Pallavi Mishra-Kalyani	OTS/OBP/DBV

1. Names:

- a. Proprietary Name: Danyelza
- b. Trade Name: Danyelza™ (naxitamab-xxxx) for intravenous use
- c. Non-Proprietary Name/USAN: Naxitamab-xxxx
- d. CAS Registry Number: 1879925-92-4
- e. Common Name: Naxitamab
- f. INN Name: Naxitamab
- g. OBP systematic name: MAB HUMANIZED (IGG1) ANTI 6450346 (GANGLIOSIDE GD2) [HU3F8]
- h. Other name(s): hu3F8, humanized 3F8

Submissions Reviewed:

Submission(s) Reviewed	Document Date (disciplines affected)
eCTD 0001/SDN 1 - Rolling Submission: Module 3 Part 1	11/27/2019 (OBP, OPMA)
eCTD 0003/SDN 3 - Rolling Submission: Module 3 Part 2	3/13/2020 (OBP, OPMA)
eCTD 0004/SDN 4 - Original BLA Submission	3/31/2020 (OBP, OPMA)
eCTD 0007/SDN 7 - Product Quality (PQ) Information Request (IR) 1	5/1/2020 (OBP, OPMA)
eCTD 0008/SDN 8 - Rolling Submission: Module 3 Part 3	5/7/2020 (OBP, OPMA)
eCTD 0009/SDN 9 - Response to AOM Meeting Discussion and PQ IR-2	5/7/2020 (OBP, OPMA)
eCTD 0013/SDN 13 - Rolling Submission: Module 3 Part 4	5/27/2020 (OBP, OPMA)
eCTD 0018/SDN 18	6/8/2020 (OPMA)
eCTD 0021/SDN 21 - PQ IR 4	6/12/2020 (OBP, OPMA)
eCTD 0023/SDN 23 - PQ IR 5	6/17/2020 (OPMA)
eCTD 0024/SDN 24 - PQ IR 6	6/19/2020 (OBP)
eCTD 0025/SDN 25 - Follow up to Rolling Submission: Module 3 Part 4	6/25/2020 (OBP, OPMA)
eCTD 0026/SDN 26 - PQ IR 7	6/26/2020 (OBP)
eCTD 0033/SDN 33 - PQ IR 8	7/9/2020 (OPMA)
eCTD 0034/SDN 34 - Update to Module 3	7/10/2020 (OBP, OPMA)
eCTD 0035/SDN 35 - PQ IR 9	7/17/2020 (OBP)
eCTD 0041/SDN 41 - PQ IR 10	8/3/2020 (OPMA)
eCTD 0042/SDN 42 - Response to Midcycle T-con	8/4/2020 (OBP)
eCTD 0050/SDN 50 - PQ IR 12	8/20/2020 (OPMA)
eCTD 0051/SDN 51 - PQ IR 11	8/7/2020 (OPMA)
eCTD 0053/SDN 53 - PQ IR 13	8/25/2020 (OBP, OPMA)
eCTD 0054/SDN 54 - Clinical IR concerning Immunogenicity	8/26/2020 (OBP)
eCTD 0060/SDN 60 - PQ IR 14	9/9/2020 (OBP, OPMA)

eCTD 0060/SDN 60 - PQ IR 15	9/9/2020 (OPMA)
eCTD 0060/SDN 60 - PQ IR 16	9/9/2020 (OBP)
eCTD 0062/SDN 62 - PQ IR 17	9/15/2020 (OBP, OPMA)
eCTD 0064/SDN 64 - PQ IR 18	9/18/2020 (OBP)
eCTD 0065/SDN 65 – PQ IR 19	9/21/2020 (OPMA)
eCTD 0069/SDN 69 – Update to Module 3	9/30/2020 (OBP, OPMA)
eCTD 0072/SDN 72 - PQ IR 20	10/6/2020 (OPMA)
eCTD 0071/SDN 71 - PQ IR 21	10/5/2020 (OBP)
eCTD 0082/SDN 85 – New microbial in-use stability study	11/5/2020 (OPMA)
eCTD 0083/SDN 86 – Labeling update	11/9/2020 (OPMA, OBP)

Quality Review 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 Review Completed
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	N/A
	III			3	Adequate	N/A
	V			2	Adequate	N/A
	III			3	Adequate	N/A

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

2. 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 reviewed).

- B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	132793	Parent IND

3. Consults: None

4. Environmental Assessment

A categorical exclusion from submitting an Environmental Assessment of naxitamab is requested per 21 CFR 25, section 25.31(c). The antibody protein product, its metabolites and degradation products occur naturally in the environment. Action on this application will not significantly alter the concentration or distribution of antibodies, their metabolites, or degradation products in the environment.

The request for categorical exclusion is granted.

Executive Summary Amendment

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval for STN 761171 for Danyelza (naxitamab). The data submitted in this application are adequate to support the conclusion that the manufacture of Danyelza (naxitamab-xxxx) 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.

The original OPQ Application Team Lead (ATL) review recommending approval was completed and signed on October 7th, 2020 in Panorama. The Sponsor submitted new microbial in-use stability data supporting a proposed in-use storage time at room temperature of 8 hours. **Specifically, the data support storage for ≤8 hours at 15-25°C.** The "Dating and Storage Period" recommendation for Naxitamab drug product (DP) in this memorandum on page 15 has been updated to reflect this change.

Additionally, the original ATL review memorandum signed into Panorama on October 7th, 2020, noted the following concerning a final recommendation on the Drug Substance (DS) facility:

At the time of this review, the OPMA assessment of the drug substance manufacturing site was not complete. Initial recommendations of approval of the facility and a post-approval inspection (PoAI) have been made, and this executive summary is filed on the assumption that these recommendations will stand from the OPMA assessment team. We expect a completed assessment by October 16th, 2020. If at that time a new recommendation is needed, we will make an addendum to this assessment.

The review of the facility was completed October 16th, 2020, and the initial recommendation of approval with a PoAI was confirmed.

B. Approval Action Letter Language:

- Manufacturing location:
 - Drug Substance:
Patheon [REDACTED] (b) (4)
 - Drug Product:
Patheon Manufacturing Services LLC, 5900 Martin Luther King Jr. Highway,
Greenville, North Carolina, The United States of America (FEI: 1018495)
- Fill size and dosage form: 40 mg in 10 mL (4 mg/mL) solution for infusion
- Dating period:
 - Drug Product: 12 months at 2 to 8°C
 - Drug Substance: (b) (4) months at (b) (4) °C
 - 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 process validation drug substance batches and drug product lots.
 - 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.
- Exempt from lot release in accordance with 21 CFR 601.2a. Naxitamab is a specified product.

C. Benefit/Risk Considerations:

Danyelza (naxitamab-xxxx) is a recombinant, humanized IgG1 κ monoclonal antibody that binds to the disialoganglioside GD2 (GD2) which is preferentially expressed on tumor cells of neuroectodermal origin. Upon binding, naxitamab induces cell killing by Fc-mediated immune responses including ADCC and CDC. Naxitamab DP is a sterile solution for infusion. Currently, there is one other FDA-approved treatment for high risk neuroblastoma that targets GD2 and induces Fc-mediated killing of target cells, Unituxin. However, the demonstrated manufacturing capabilities and the availability of more treatment options for the subset of high-risk neuroblastoma patients included in the indication of naxitamab warrants approval of this product alongside the existing treatment options.

Review of manufacturing has identified that the methodologies used for DS and DP manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The Sponsor has agreed to the post marketing commitments (PMCs) listed below and protocols to determine the need for any additional controls to supplement the license for future naxitamab production as part of lifecycle management. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. We also recommend approval of the commercial manufacture of naxitamab DS at Patheon (b) (4) and of naxitamab DP at Patheon Manufacturing Services LLC, Greenville, North Carolina, USA. The OBP (Office of Biotechnology Products) product quality and immunogenicity assay assessments, OPMA (Office of Pharmaceutical Manufacturing Assessment) DS and DP microbiological and facility assessments, and OBP labeling technical assessments are located as separate documents in Panorama.

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

- 1) Conduct an analysis of the clonality of the naxitamab master cell bank using a suitable method such as "Next Generation Sequencing". Report submit date: April 2021.
- 2) Perform an additional in-use compatibility study with the specific purpose of testing aggregation and particulates. Samples from the in-use study will also be tested for visible particles and subvisible particles. Data will be available in May 2021 and reported in an annual report for the period covering May 2021.
- 3) Submit the validation report for the helium leak container closure integrity testing (b) (4) Due October 2020.

- 4) Perform container closure integrity testing on at least 500 units from one lot of drug product using the helium leak method, which is sensitive enough to detect breaches (b) (4) μm in size. Due December 2020.
- 5) Submit bioburden method verification data with testing volume of 100 mL for three drug product batches. Due February 2021.
- 6) Repeat the bacterial retention study with naxitamab drug product to include measurement of (b) (4). Implement routine monitoring of (b) (4) and include a (b) (4) parameter for sterile filtration. Submit a report that includes (b) (4) results from three drug product batches. Due December 2021.
- 7) Provide data to demonstrate that shipping temperature is maintained within the shippers for drug product when exposed to worst-case conditions of temperature (summer and winter). Due October 2020.
- 8) Conduct a low endotoxin recovery study at process relevant temperature (b) (4) and duration to ensure the release test method can reliably detect endotoxin in naxitamab drug product. In case the study shows endotoxin recovery below 50% at process relevant conditions, develop an alternative endotoxin testing method to mitigate LER. Due November 2020.

II. Summary of Quality Assessments:

A. COA Identification, Risk and Lifecycle Knowledge Management

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Concentration	Efficacy	(b) (4)	(b) (4)	The validation data provided to date support consistent concentration in manufacture. The final validation report is expected with the first annual report.
Identity	Efficacy and Safety	Intrinsic to the molecule	(b) (4)	N/A
(b) (4)	Efficacy	(b) (4)	(b) (4)	(b) (4)

				(b) (4)
Glycosylation	Efficacy (potency)	Primarily upstream manufacturing process	(b) (4)	
Aggregates (high molecular weight species)	Safety (immunogenicity)	Manufacturing process, environmental stresses		N/A
Fragments (low molecular weight species)	Efficacy	Manufacturing process, environmental stresses		(b) (4)
Appearance	Stability	Formulation components and stability		N/A

B. Drug Substance (naxitamab) Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: DS CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Endotoxin (contaminant)	Safety and Purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process.	(b) (4)	N/A
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by	Bioburden can be introduced by raw materials and throughout the		N/A

	contaminating microorganisms)	manufacturing process.	(b) (4)	
Host Cell Protein (Process related impurity)	Safety (Immunogenicity)	Production cell line		N/A
Host cell DNA (Process related impurity)	Safety	Production cell line		N/A
Adventitious Agents (TSE, virus, mycoplasma)	Safety (systemic infection)	Starting materials, raw materials, cell bank, (b) (4)		N/A
(b) (4)	Safety	Manufacturing process		N/A
	Safety	Manufacturing Process		N/A
	Safety	Manufacturing Process		N/A
Leachables (Process-related impurity)	Safety and Stability	From manufacturing contact material and the DS container closure system (CCS)		(b) (4)

(b) (4)	Safety	(b) (4)	(b) (4) Levels are below toxicological concern based on the risk assessment.
Elemental impurities	Safety		N/A

- **Description:**
Danyelza (naxitamab-xxxx) is a recombinant, humanized IgG1κ monoclonal antibody with an approximate molecular weight of 144 kDa. Naxitamab is produced using CHO cells engineered to express the protein followed by standard monoclonal antibody purification techniques. The glycosylation profile of naxitamab is consistent with expected IgG1κ monoclonal antibodies. Naxitamab is administered in combination with GM-CSF in patients with relapsed/refractory high-risk neuroblastoma originating in bone or bone marrow.
- **Mechanism of Action (MoA):**
Naxitamab binds to GD2 which is preferentially expressed on tumor cells of neuroectodermal origin. Upon binding, naxitamab induces cell killing by Fc-mediated immune responses through utilization of the C1q component of the complement cascade inducing CDC and FcγRII/FcγRIII effector functions including ADCC.
- **Potency Assay:**
There are four potency assays utilized to ensure the potency of naxitamab:
 - Binding to the target GD2 is assessed by ELISA with recombinant GD2 as the bait and determination of binding by detection antibody (peroxide-conjugated Goat anti-human IgG). Potency is reported relative to the reference standard (RS) in each assay.
 - CDC activity is assessed using LAN-1 cells (a human GD2+ neuroblastoma cell line). Naxitamab is incubated with the LAN-1 cells and complement factor is added. CDC activity is determined by measurement of the cell death of LAN-1 cells through ATP measurement of the remaining viable cells. Potency is reported relative to the RS in each assay.
 - Activation of FcγRIIa and FcγRIIIa induced ADCC activity is controlled by a (b) (4)
 - Additional analysis of FcγRIIa and FcγRIIIa activity is performed using a commercially available antibody dependent cellular phagocytosis (ADCP) assay. The assay utilizes LAN-1 cells as with the CDC assay. Naxitamab is combined

with the LAN-1 cells, engaging the GD2 epitope. Engineered Jurkat cells which express luciferase in response to FcγRIIa binding and activation are then added to the naxitamab and LAN-1 cell mix. Fc engagement is measured by the resulting luciferase production. Naxitamab potency is reported relative to the RS in each assay.

Additional control of ADCC function is provided through [REDACTED] (b) (4)

[REDACTED]
Validation of the above potency assays was performed with RS and DS batches with the intended commercial formulation. The potency of naxitamab for all four assays is determined in comparison to a RS.

- Reference Materials:

[REDACTED] (b) (4)

- Critical Starting Materials or Intermediates:

[REDACTED] (b) (4)

- Manufacturing Process Summary:

[REDACTED] (b) (4)



(b) (4)

- Container Closure:
Naxitamab DS is stored (b) (4)
- Dating Period and Storage Conditions:
The dating period for the DS is (b) (4) months when stored at (b) (4) °C. The sponsor is monitoring stability of the naxitamab DS (b) (4)

C. Drug Product (naxitamab) Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for DP COAs that derive from the DP manufacturing process and general DP attributes.

Table 3: DP COA Identification, Risk, and Lifecycle Management

COA (Type)	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process or failure of container closure integrity	(b) (4)	N/A
Endotoxin (contaminant)	Safety, Purity, and Immunogenicity	Raw materials, contamination may be introduced throughout the DP	(b) (4)	N/A

		manufacturing process	(b) (4)
Container closure integrity (contaminant)	Safety (maintenance of sterility during shelf-life or evaporation/leakage impacting concentration or content)	Container closure breaches during storage	N/A
Concentration	Efficacy	Manufacturing process	(b) (4)
Visual Appearance and Particles	Safety (immunogenicity), Stability	Manufacturing process, DS substance and sheer stresses during DP manufacturing	N/A
(b) (4)	Efficacy	DS, manufacturing process	Refer to further description in DS CQA table above.
Glycosylation	Stability	DS, manufacturing process	Refer to further description in DS CQA table above.
pH	Efficacy and stability	Formulation components and stability	N/A
Osmolality (General)	Stability	Composition of the DP	N/A
Volume in container (General)	Efficacy/Dosing	(b) (4)	N/A
Particulate matter for subvisible particles (Product or process related impurities)	Safety and Immunogenicity	Manufacturing process and CCS, subvisible particles could be product or foreign particles	N/A
Elemental Impurities	Safety (Toxicity)	From product contact material	N/A

		during manufacturing and storage	(b) (4)
Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS	The risk is deemed to be low, and the real-time study will be submitted as part of subsequent annual reports.

- Potency and Strength:**
Naxitamab is provided as 40 mg in 10 mL (4 mg/mL) solution for intravenous use. The strength of naxitamab is 4 mg/mL. Potency is defined relative to the current naxitamab RS and incorporates GD2-binding, CDC activity, FcγRIIIa (CD16) binding and ADCP. The potency assays are the same as described in the DS section of this memo.
- Summary of Product Design:**
Naxitamab is supplied as 10 mL of 4 mg/mL solution for intravenous use. Sufficient overfill to ensure dose delivery has been demonstrated (b) (4)
- List of Excipients:**
The naxitamab DP excipients per 10 mL solution are (b) (4) sodium citrate (62.6 mg), citric acid (7.1 mg), sodium chloride (70.1 mg), poloxamer 188 (b) (4) 15 mg and sufficient water for injection to a total volume of 10 mL.
- Reference Materials:**
The same RS are used for DS and DP.
- Manufacturing Process Summary:**
(b) (4)

- Container Closure:

The primary container closure system for naxitamab DP consists of 10 mL (b) (4) glass vials with 20 mm (b) (4) stoppers and a 20 mm flip-off aluminum (b) (4) seal.

Compatibility studies for naxitamab DP administration utilizing 5% HSA (USP grade) and 0.9% Sodium Chloride Injection (USP grade) were provided confirming the maintenance of potency and concentration through the intended route of administration for intravenous infusion. The Sponsor has committed to additional studies to assess purity of the administered naxitamab DP by assessment of aggregates and particulates with the report to be submitted in an annual report.

- Dating Period and Storage Conditions:

The dating period for naxitamab DP is 12 months when stored at 2-8°C. The in-use compatibility and stability data included in the BLA support the maintenance of potency and concentration after preparation for infusion with 5% HSA (USP grade) for up to 12 hours when stored at temperatures below 25°C or up to 24 hours in the refrigerator at 2-8°C. During the original submission review cycle, the Sponsor provided microbial in-use data supporting 24 hours of storage at 2-8°C after preparation. In the updated microbial in-use stability study provided November 5th, 2020, the sponsor provided data to support ≤8 hours of storage at 15-25°C. Therefore, the recommended in-use period in the label for the naxitamab DP is up to 8 hours at 15-25°C, and up to 24 hours at 2-8°C. The Sponsor has committed to provide additional data assessing the aggregates and particulates of naxitamab DP in the in-use conditions.

- Commercial Presentation:

The intended commercial presentation will be a single-dose vial containing 40 mg/10 mL (4 mg/mL) naxitamab as a clear to slightly opalescent and colorless to slightly yellow solution for intravenous use.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

- Store in a refrigerator at 2°C to 8°C
- Protect from light by storing in the outer carton

F. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
(b) (4)	Patheon (b) (4)	FEI: (b) (4)	Approve Based on 704(a)(4) Records Review	N/A	Approve
Manufacture of drug substance (b) (4)		DUNS: (b) (4)			

(b) (4)				
	(b) (4)	No Evaluation Necessary	N/A	N/A
		Approved Based on Previous History	N/A	Approve
		No Evaluation Necessary	N/A	N/A
		No Evaluation Necessary	N/A	N/A
		Approve Based on Previous History	N/A	Approve
		Approve Based on Previous History	N/A	Approve
		Approve Based on Previous History	N/A	Approve
		Approve Based on Previous History	N/A	Approve
		Approve Based on Previous History	N/A	Approve

(b) (4)			
	Approve Based on Previous History	N/A	Approve
	Approve Based on Previous History	N/A	Approve
	No Evaluation Necessary	N/A	N/A
	Approve Based on Pre-license Inspection (PLI)	See table below	Approve

DRUG PRODUCT

Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture of final naxitamab drug product (b) (4) (b) (4)	Patheon Manufacturing Services LLC, 5900 Martin Luther King Jr. HWY Greenville, NC 27834, USA	FEI: 1018495 DUNS: 079415560	Approve Based on PLI	(b) (4)	Approve EIR and firm's responses were reviewed and deemed acceptable. CDER/OPMA concurs with the approval recommendation.
(b) (4)			Approve Based on 704(a)(4) Records Review	N/A	Approve

(b) (4)					
(b) (4)			Approved Based on Previous History	N/A	Approve
			Approved Based on Previous History	N/A	Approve
			Approved Based on Previous History	N/A	Approve
			Approved Based on Previous History	N/A	Approve
Final Product Release	Y-mAbs Therapeutics A/S Agern Allé 11, DK-2970 Hoersholm, Denmark	Authorization No.: 36392	No Evaluation Necessary	N/A	N/A

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, process equipment cleaning, and contamination control strategy were provided for Patheon (b) (4) and Patheon Manufacturing Services LLC, Greenville, NC (FEI 1018495) proposed for Naxitamab DS and DP manufacturing, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspection coverage. This submission is recommended for approval from a facilities perspective.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

(b) (4)

- ii. Outstanding review issues/residual risk: None
- iii. Future inspection points to consider: PoAI recommended for Patheon

(b) (4)

b. Drug Product

- i. Protocols approved:

(b) (4)

- ii. Outstanding review issues/residual risk: The sponsor has committed to provide the remaining results of the final DS PPQ batch and final DS PPQ validation report in a BLA supplement. This arrangement was agreed to in a pre-BLA meeting with the Agency. Ranges for process parameters, existing protocols, and supportive data should be considered in light of the final PPQ report.
- iii. Future inspection points to consider: PoAI recommended for Patheon Manufacturing Services LLC, Greenville, NC (FEI 1018495)

Quality Assessment Summary Tables
Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/source material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non-Primate Mammalian Cell Substrate/source material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal source		X	
9.	Transgenic Plant source		X	
10.	New Molecular Entity	X		
11.	PEPFAR drug		X	
12.	PET drug		X	
13.	Sterile Drug Product	X		
14.	Other: [fill in information]		X	
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]		X	
16.	Comparability Protocol(s)		X	
17.	End of Phase II/Pre-NDA Agreements		X	
18.	SPOTS (special products on-line tracking system)		X	
19.	USAN assigned name	X		
20.	Other [fill in]		X	
Quality Considerations				
21.	Drug Substance Overage		X	
22.	Design Space	Formulation		X
23.		Process		X
24.		Analytical Methods		X
25.		Other		X
26.	Other QbD Elements		X	
27.	Real Time release testing (RTRT)		X	
28.	Parametric release in lieu of Sterility testing		X	
29.	Alternative Microbiological test methods		X	
30.	Process Analytical Technology in Commercial Production		X	
31.	Non-compendial analytical procedures	Drug Product	X	
32.		Excipients		X
33.		Drug Substance	X	
34.	Excipients	Human or Animal Origin		X
35.		Novel		X
36.	Nanomaterials		X	
37.	Genotoxic Impurities or Structural Alerts		X	
38.	Continuous Manufacturing		X	
39.	Use of Models for Release		X	
40.	Other {fill-in}	X		
	The sponsor obtained agreement to perform a rolling submission of BLA components, including a sequential approach to process validation. The sponsor submitted the first DS PPQ batch information with the original submission, the second DS PPQ batch prior to the midcycle and has committed to provide the final DS PPQ batch in post-approval submission along with the final DS validation report.			



Brian
Roelofs

Digitally signed by Brian Roelofs
Date: 11/13/2020 01:16:34PM
GUID: 57f29d150070ca84f102970a51133e31



William
Hallett

Digitally signed by William Hallett
Date: 11/13/2020 01:17:29PM
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First Approval for Indication

Recommendation: BLA Approval

At the time of this review, the OPMA assessment of the drug substance manufacturing site was not complete. Initial recommendations of approval of the facility and a post-approval inspection (PoAI) have been made, and this executive summary is filed on the assumption that these recommendations will stand from the OPMA assessment team. We expect a completed assessment by October 16th, 2020. If at that time a new recommendation is needed, we will make an addendum to this assessment.

BLA Number: 761171
Review Number: 1
Review Date: October 7th, 2020

Drug Name/Dosage Form	Danyelza (naxitamab-xxxx) for intravenous use
Strength/Potency	4.0 mg/mL (40 mg/10 mL) single dose vial
Route of Administration	Intravenous use
Rx/OTC dispensed	Rx
Indication	Treatment of refractory or relapsed high-risk neuroblastoma in bone (b) (4) or bone marrow in combination with GM-CSF
Applicant/Sponsor	Y-mAbs Therapeutics, Inc.

Product Overview

Danyelza (naxitamab-xxxx) is a recombinant, humanized IgG1 κ monoclonal antibody with an approximate molecular weight of 144 kilodaltons that is produced using Chinese Hamster Ovary (CHO) cells. Naxitamab binds to the disialoganglioside GD2 (GD2), which is preferentially expressed on tumor cells of neuroectodermal origin. Upon binding, naxitamab induces cell killing by Fc-mediated immune responses including antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Naxitamab drug product (DP) is a sterile solution for infusion. Each vial of naxitamab DP contains 4.0 mg/mL of naxitamab in (b) (4) consisting of 62.6 mg sodium citrate, 7.1 mg anhydrous citric acid, 70.1 mg sodium chloride, 15 mg Poloxamer 188 (b) (4) and water for injection. Each DP vial contains a total volume of (b) (4). The treatment regimen is 3 mg/kg/day, infused three times per cycle on days 1, 3 and 5 (b) (4). (b) (4) GM-CSF is administered on the 5 days preceding the first infusion of naxitamab-xxxx at a dose of 250 μ g/m²/day.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance (DS)	Ian McWilliams	OPQ/OBP/DBRRII
DP	Ian McWilliams	OPQ/OBP/DBRRII
Immunogenicity	Ian McWilliams	OPQ/OBP/DBRRII
Labeling	Vicky Borders Hemphill Ian McWilliams	OPQ/OBP OPQ/OBP/DBRRII
DS Micro and Facilities	Viviana Matta	OPQ/OPMA/DBM2
DP Micro and Facilities	Yun Wu	OPQ/OPMA/DBM2
RBPM	Anika Lalmansingh	OPQ/OPRO
Team Lead	Brian Roelofs Maxwell Van Tassell (DS Micro)	OPQ/OBP/DBRRII OPQ/OPMA/DBM1

	Virginia Carroll (DP Micro) Zhihao (Peter) Qiu (Facilities)	OPQ/OPMA/DBM2 OPQ/OPMA/DBM
Application Technical Lead	Brian Roelofs	OPQ/OBP/DBRRII

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Rebecca Cohen	OND/ORO/DROOD
Cross-disciplinary Team Lead	Amy Barone	OND/OOD/DOII
Medical Officer	Diana Bradford	OND/OOD/DOII
Pharm/Tox	Stephanie Aungst/Whitney Helms	OND/OOD/DHOT
Clinical Pharmacology	Catharine Bulik/Hong Zhao	OTS/OCP/DCPI
Statistics	Xiaoxue Li/Pallavi Mishra-Kalyani	OTS/OBP/DBV

1. Names:

- a. Proprietary Name: Danyelza
- b. Trade Name: Danyelza™ (naxitamab-xxxx) for intravenous use
- c. Non-Proprietary Name/USAN: Naxitamab-xxxx
- d. CAS Registry Number: 1879925-92-4
- e. Common Name: Naxitamab
- f. INN Name: Naxitamab
- g. OBP systematic name: MAB HUMANIZED (IGG1) ANTI 6450346 (GANGLIOSIDE GD2) [HU3F8]
- h. Other name(s): hu3F8, humanized 3F8

Submissions Reviewed:

Submission(s) Reviewed	Document Date (disciplines affected)
eCTD 0001/SDN 1 - Rolling Submission: Module 3 Part 1	11/27/2019 (OBP, OPMA)
eCTD 0003/SDN 3 - Rolling Submission: Module 3 Part 2	3/13/2020 (OBP, OPMA)
eCTD 0004/SDN 4 - Original BLA Submission	3/31/2020 (OBP, OPMA)
eCTD 0007/SDN 7 - Product Quality (PQ) Information Request (IR) 1	5/1/2020 (OBP, OPMA)
eCTD 0008/SDN 8 - Rolling Submission: Module 3 Part 3	5/7/2020 (OBP, OPMA)
eCTD 0009/SDN 9 - Response to AOM Meeting Discussion and PQ IR-2	5/7/2020 (OBP, OPMA)
eCTD 0013/SDN 13 - Rolling Submission: Module 3 Part 4	5/27/2020 (OBP, OPMA)
eCTD 0018/SDN 18	6/8/2020 (OPMA)
eCTD 0021/SDN 21 - PQ IR 4	6/12/2020 (OBP, OPMA)
eCTD 0023/SDN 23 - PQ IR 5	6/17/2020 (OPMA)
eCTD 0024/SDN 24 - PQ IR 6	6/19/2020 (OBP)
eCTD 0025/SDN 25 - Follow up to Rolling Submission: Module 3 Part 4	6/25/2020 (OBP, OPMA)
eCTD 0026/SDN 26 - PQ IR 7	6/26/2020 (OBP)
eCTD 0033/SDN 33 - PQ IR 8	7/9/2020 (OPMA)
eCTD 0034/SDN 34 - Update to Module 3	7/10/2020 (OBP, OPMA)
eCTD 0035/SDN 35 - PQ IR 9	7/17/2020 (OBP)
eCTD 0041/SDN 41 - PQ IR 10	8/3/2020 (OPMA)
eCTD 0042/SDN 42 - Response to Midcycle T-con	8/4/2020 (OBP)

eCTD 0050/SDN 50 - PQ IR 12	8/20/2020 (OPMA)
eCTD 0051/SDN 51 - PQ IR 11	8/7/2020 (OPMA)
eCTD 0053/SDN 53 - PQ IR 13	8/25/2020 (OBP, OPMA)
eCTD 0054/SDN 54 - Clinical IR concerning Immunogenicity	8/26/2020 (OBP)
eCTD 0060/SDN 60 - PQ IR 14	9/9/2020 (OBP, OPMA)
eCTD 0060/SDN 60 - PQ IR 15	9/9/2020 (OPMA)
eCTD 0060/SDN 60 - PQ IR 16	9/9/2020 (OBP)
eCTD 0062/SDN 62 - PQ IR 17	9/15/2020 (OBP, OPMA)
eCTD 0064/SDN 64 - PQ IR 18	9/18/2020 (OBP)
eCTD 0065/SDN 65 – PQ IR 19	9/21/2020 (OPMA)
eCTD 0069/SDN 69 – Update to Module 3	9/30/2020 (OBP, OPMA)
eCTD 0072/SDN 72 - PQ IR 20	10/6/2020 (OPMA)
eCTD 0071/SDN 71 - PQ IR 21	10/5/2020 (OBP)

Quality Review 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 Review Completed
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	N/A
	III			3	Adequate	N/A
	V			2	Adequate	N/A
	III			3	Adequate	N/A

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

2. 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 reviewed).

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description

IND	132793	Parent IND

3. Consults: None

4. Environmental Assessment

A categorical exclusion from submitting an Environmental Assessment of naxitamab is requested per 21 CFR 25, section 25.31(c). The antibody protein product, its metabolites and degradation products occur naturally in the environment. Action on this application will not significantly alter the concentration or distribution of antibodies, their metabolites, or degradation products in the environment.

The request for categorical exclusion is granted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval for STN 761171 for Danyelza (naxitamab). The data submitted in this application are adequate to support the conclusion that the manufacture of Danyelza (naxitamab-xxxx) 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.

B. Approval Action Letter Language:

- Manufacturing location:
 - Drug Substance:
Patheon [REDACTED] (b) (4)
 - Drug Product:
Patheon Manufacturing Services LLC, 5900 Martin Luther King Jr. Highway,
Greenville, North Carolina, The United States of America (FEI: 1018495)
- Fill size and dosage form: 40 mg in 10 mL (4 mg/mL) solution for infusion
- Dating period:
 - Drug Product: 12 months at 2 to 8°C
 - Drug Substance: (b) (4) months at [REDACTED] (b) (4)°C
 - 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 process validation drug substance batches and drug product lots.
 - 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.
- Exempt from lot release in accordance with 21 CFR 601.2a. Naxitamab is a specified product.

C. Benefit/Risk Considerations:

Danyelza (naxitamab-xxxx) is a recombinant, humanized IgG1 κ monoclonal antibody that binds to the disialoganglioside GD2 (GD2) which is preferentially expressed on tumor cells of neuroectodermal origin. Upon binding, naxitamab induces cell killing by Fc-mediated immune responses including ADCC and CDC. Naxitamab DP is a sterile solution for infusion. Currently, there is one other FDA-approved treatment for high risk neuroblastoma that targets GD2 and induces Fc-mediated killing of target cells, Unituxin. However, the demonstrated manufacturing capabilities and the availability of more treatment options for the subset of high-risk

neuroblastoma patients included in the indication of naxitamab warrants approval of this product alongside the existing treatment options.

Review of manufacturing has identified that the methodologies used for DS and DP manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The Sponsor has agreed to the post marketing commitments (PMCs) listed below and protocols to determine the need for any additional controls to supplement the license for future naxitamab production as part of lifecycle management. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. We also recommend approval of the commercial manufacture of naxitamab DS at Patheon (b) (4) and of naxitamab DP at Patheon Manufacturing Services LLC, Greenville, North Carolina, USA. The OBP (Office of Biotechnology Products) product quality and immunogenicity assay assessments, OPMA (Office of Pharmaceutical Manufacturing Assessment) DS and DP microbiological and facility assessments, and OBP labeling technical assessments are located as separate documents in Panorama.

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

- 1) Conduct an analysis of the clonality of the naxitamab master cell bank using a suitable method such as "Next Generation Sequencing". Report submit date: April 2021.
- 2) Perform an additional in-use compatibility study with the specific purpose of testing aggregation and particulates. Samples from the in-use study will also be tested for visible particles and subvisible particles. Data will be available in May 2021 and reported in an annual report for the period covering May 2021.
- 3) Submit the validation report for the helium leak container closure integrity testing (b) (4) Due October 2020.
- 4) Perform container closure integrity testing on at least 500 units from one lot of drug product using the helium leak method, which is sensitive enough to detect breaches $\leq$ (b) (4) μm in size. Due December 2020.
- 5) Submit bioburden method verification data with testing volume of 100 mL for three drug product batches. Due February 2021.
- 6) Repeat the bacterial retention study with naxitamab drug product to include measurement of (b) (4) Implement routine monitoring of (b) (4) and include a (b) (4) parameter for sterile filtration. Submit a report that includes (b) (4) results from three drug product batches. Due December 2021.
- 7) Provide data to demonstrate that shipping temperature is maintained within the shippers for drug product when exposed to worst-case conditions of temperature (summer and winter). Due October 2020.

- 8) Conduct a low endotoxin recovery study at process relevant temperature (b) (4) and duration to ensure the release test method can reliably detect endotoxin in naxitamab drug product. In case the study shows endotoxin recovery below 50% at process relevant conditions, develop an alternative endotoxin testing method to mitigate LER. Due November 2020.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Concentration	Efficacy	(b) (4)	(b) (4)	The validation data provided to date support consistent concentration in manufacture. The final validation report is expected with the first annual report.
Identity	Efficacy and Safety	Intrinsic to the molecule	(b) (4)	N/A
(b) (4)	Efficacy	(b) (4)	(b) (4)	(b) (4)
Glycosylation	Efficacy (potency)	(b) (4)	(b) (4)	(b) (4)

Aggregates (high molecular weight species)	Safety (immunogenicity)	Manufacturing process, environmental stresses	(b) (4)	N/A
Fragments (low molecular weight species)	Efficacy	Manufacturing process, environmental stresses	(b) (4)	(b) (4)
Appearance	Stability	Formulation components and stability		N/A

B. Drug Substance (naxitamab) Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: DS CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Endotoxin (contaminant)	Safety and Purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process.	(b) (4)	N/A
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process.		N/A
Host Cell Protein (Process related impurity)	Safety (Immunogenicity)	Production cell line		N/A
Host cell DNA (Process related impurity)	Safety	Production cell line		N/A
Adventitious Agents (TSE, virus, mycoplasma)	Safety (systemic infection)	Starting materials, raw materials, cell bank, (b) (4)		N/A

			(b) (4)	
(b) (4)	Safety	Manufacturing process		N/A
	Safety	Manufacturing Process		N/A
	Safety	Manufacturing Process		N/A
Leachables (Process-related impurity)	Safety and Stability	From manufacturing contact material and the DS container closure system (CCS)		(b) (4)
(b) (4)	Safety	(b) (4)		Levels are below toxicological concern based on the risk assessment.
Elemental impurities	Safety			N/A

- **Description:**
Danyelza (naxitamab-xxxx) is a recombinant, humanized IgG1κ monoclonal antibody with an approximate molecular weight of 144 kDa. Naxitamab is produced using CHO

cells engineered to express the protein followed by standard monoclonal antibody purification techniques. The glycosylation profile of naxitamab is consistent with expected IgG1 κ monoclonal antibodies. Naxitamab is administered in combination with GM-CSF in patients with relapsed/refractory high-risk neuroblastoma originating in bone or bone marrow.

- Mechanism of Action (MoA):
Naxitamab binds to GD2 which is preferentially expressed on tumor cells of neuroectodermal origin. Upon binding, naxitamab induces cell killing by Fc-mediated immune responses through utilization of the C1q component of the complement cascade inducing CDC and Fc γ RII/Fc γ RIII effector functions including ADCC.
- Potency Assay:
There are four potency assays utilized to ensure the potency of naxitamab:
 - Binding to the target GD2 is assessed by ELISA with recombinant GD2 as the bait and determination of binding by detection antibody (peroxide-conjugated Goat anti-human IgG). Potency is reported relative to the reference standard (RS) in each assay.
 - CDC activity is assessed using LAN-1 cells (a human GD2+ neuroblastoma cell line). Naxitamab is incubated with the LAN-1 cells and complement factor is added. CDC activity is determined by measurement of the cell death of LAN-1 cells through ATP measurement of the remaining viable cells. Potency is reported relative to the RS in each assay.
 - Activation of Fc γ RIIa and Fc γ RIIIa induced ADCC activity is controlled by a (b) (4)

 - Additional analysis of Fc γ RIIa and Fc γ RIIIa activity is performed using a commercially available antibody dependent cellular phagocytosis (ADCP) assay. The assay utilizes LAN-1 cells as with the CDC assay. Naxitamab is combined with the LAN-1 cells, engaging the GD2 epitope. Engineered Jurkat cells which express luciferase in response to Fc γ RIIa binding and activation are then added to the naxitamab and LAN-1 cell mix. Fc engagement is measured by the resulting luciferase production. Naxitamab potency is reported relative to the RS in each assay.

Additional control of ADCC function is provided through (b) (4)


Validation of the above potency assays was performed with RS and DS batches with the intended commercial formulation. The potency of naxitamab for all four assays is determined in comparison to a RS.

- Reference Materials:
 (b) (4)

(b) (4)

- Critical Starting Materials or Intermediates:

(b) (4)

- Manufacturing Process Summary:

(b) (4)

(b) (4)

- Container Closure:
Naxitamab DS is stored (b) (4)
- Dating Period and Storage Conditions:
The dating period for the DS is (b) (4) months when stored at (b) (4) °C. The sponsor is monitoring stability of the naxitamab DS (b) (4)

C. Drug Product (naxitamab) Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for DP CQAs that derive from the DP manufacturing process and general DP attributes.

Table 3: DP CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process or failure of container closure integrity	(b) (4)	N/A
Endotoxin (contaminant)	Safety, Purity, and Immunogenicity	Raw materials, contamination may be introduced throughout the DP manufacturing process		N/A
Container closure integrity (contaminant)	Safety (maintenance of sterility during shelf-life or evaporation/leakage impacting concentration or content)	Container closure breaches during storage		N/A
Concentration	Efficacy	Manufacturing process		(b) (4)

Visual Appearance and Particles	Safety (immunogenicity), Stability	Manufacturing process, DS substance and sheer stresses during DP manufacturing	(b) (4)	N/A
(b) (4)	Efficacy	DS, manufacturing process		Refer to further description in DS CQA table above.
Glycosylation	Stability	DS, manufacturing process		Refer to further description in DS CQA table above.
pH	Efficacy and stability	Formulation components and stability		N/A
Osmolality (General)	Stability	Composition of the DP		N/A
Volume in container (General)	Efficacy/Dosing	(b) (4)		N/A
Particulate matter for subvisible particles (Product or process related impurities)	Safety and Immunogenicity	Manufacturing process and CCS, subvisible particles could be product or foreign particles		N/A
Elemental Impurities	Safety (Toxicity)	From product contact material during manufacturing and storage		N/A

Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS	(b) (4)	The risk is deemed to be low, and the real-time study will be submitted as part of subsequent annual reports.

- Potency and Strength:**
 Naxitamab is provided as 40 mg in 10 mL (4 mg/mL) solution for intravenous use. The strength of naxitamab is 4 mg/mL. Potency is defined relative to the current naxitamab RS and incorporates GD2-binding, CDC activity, FcγRIIIa (CD16) binding and ADCP. The potency assays are the same as described in the DS section of this memo.

- Summary of Product Design:**
 Naxitamab is supplied as 10 mL of 4 mg/mL solution for intravenous use. Sufficient overfill to ensure dose delivery has been demonstrated (b) (4)

- List of Excipients:**
 The naxitamab DP excipients per 10 mL solution are (b) (4) sodium citrate (62.6 mg), citric acid (7.1 mg), sodium chloride (70.1 mg), poloxamer 188 (b) (4) 15 mg and sufficient water for injection to a total volume of 10 mL.

- Reference Materials:**
 The same RS are used for DS and DP.

- Manufacturing Process Summary:**

(b) (4)

- Container Closure:**

The primary container closure system for naxitamab DP consists of 10 mL (b) (4) glass vials with 20 mm (b) (4) stoppers and a 20 mm flip-off aluminum (b) (4) seal.

Compatibility studies for naxitamab DP administration utilizing 5% HSA (USP grade) and 0.9% Sodium Chloride Injection (USP grade) were provided confirming the maintenance of potency and concentration through the intended route of administration for intravenous infusion. The Sponsor has committed to additional studies to assess purity of the administered naxitamab DP by assessment of aggregates and particulates with the report to be submitted in an annual report.

- Dating Period and Storage Conditions:**
 The dating period for naxitamab DP is 12 months when stored at 2-8°C. The in-use compatibility and stability data included in the BLA support the maintenance of potency and concentration after preparation for infusion with 5% HSA (USP grade) for up to 12 hours when stored at temperatures below 25°C or up to 24 hours in the refrigerator at 2-8°C. The sponsor has provided in use microbial safety data to support 24 hours at 2-8°C after preparation. Therefore, the recommended in use period in the label for the naxitamab DP is up to 4 hours at 15-25°C, and up to 24 hours at 2-8°C. The Sponsor has committed to provide additional data assessing the aggregates and particulates of naxitamab DP in the in-use conditions.
- Commercial Presentation:**
 The intended commercial presentation will be a single-dose vial containing 40 mg/10 mL (4 mg/mL) naxitamab as a clear to slightly opalescent and colorless to slightly yellow solution for intravenous use.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

- Store in a refrigerator at 2°C to 8°C
- Protect from light by storing in the outer carton

F. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
(b) (4)	Patheon (b) (4)	FEI: (b) (4)	Approve Based on 704(a)(4) Records Review	N/A	Approve
Manufacture of drug substance		DUNS: (b) (4)			
(b) (4)					
Testing of:					

(b) (4)	(b) (4)				
		(b) (4)	No Evaluation Necessary	N/A	N/A
		(b) (4)	Approved Based on Previous History	N/A	Approve
		(b) (4)	No Evaluation Necessary	N/A	N/A



(b) (4)

No Evaluation Necessary	N/A	N/A
Approve Based on Previous History	N/A	Approve
Approve Based on Previous History	N/A	Approve
Approve Based on Previous History	N/A	Approve
Approve Based on Previous History	N/A	Approve
Approve Based on Previous History	N/A	Approve
Approve Based on Previous History	N/A	Approve
Approve Based on Previous History	N/A	Approve
Approve Based on Previous History	N/A	Approve
No Evaluation Necessary	N/A	N/A

	Austria	DUNS: 300479984 (b) (4)			
			Approve Based on Pre-license Inspection (PLI)	See table below	Approve
			DRUG PRODUCT		
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture of final naxitamab drug product (b) (4) (b) (4)	Patheon Manufacturing Services LLC, 5900 Martin Luther King Jr. HWY Greenville, NC 27834, USA	FEI: 1018495 DUNS: 079415560	Approve Based on PLI	(b) (4)	Approve EIR and firm's responses were reviewed and deemed acceptable. CDER/OPMA concurs with the approval recommendation.
			Approve Based on 704(a)(4) Records Review	N/A	Approve
			Approved Based on Previous History	N/A	Approve
			Approved Based on Previous History	N/A	Approve

(b) (4)			Approved Based on Previous History	N/A	Approve
			Approved Based on Previous History	N/A	Approve
Final Product Release	Y-mAbs Therapeutics A/S Agern Allé 11, DK-2970 Hoersholm, Denmark	Authorization No.: 36392	No Evaluation Necessary	N/A	N/A

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, process equipment cleaning, and contamination control strategy were provided for Patheon (b) (4) and Patheon Manufacturing Services LLC, Greenville, NC (FEI 1018495) proposed for Naxitamab DS and DP manufacturing, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspection coverage. This submission is recommended for approval from a facilities perspective.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

(b) (4)					

(b) (4)

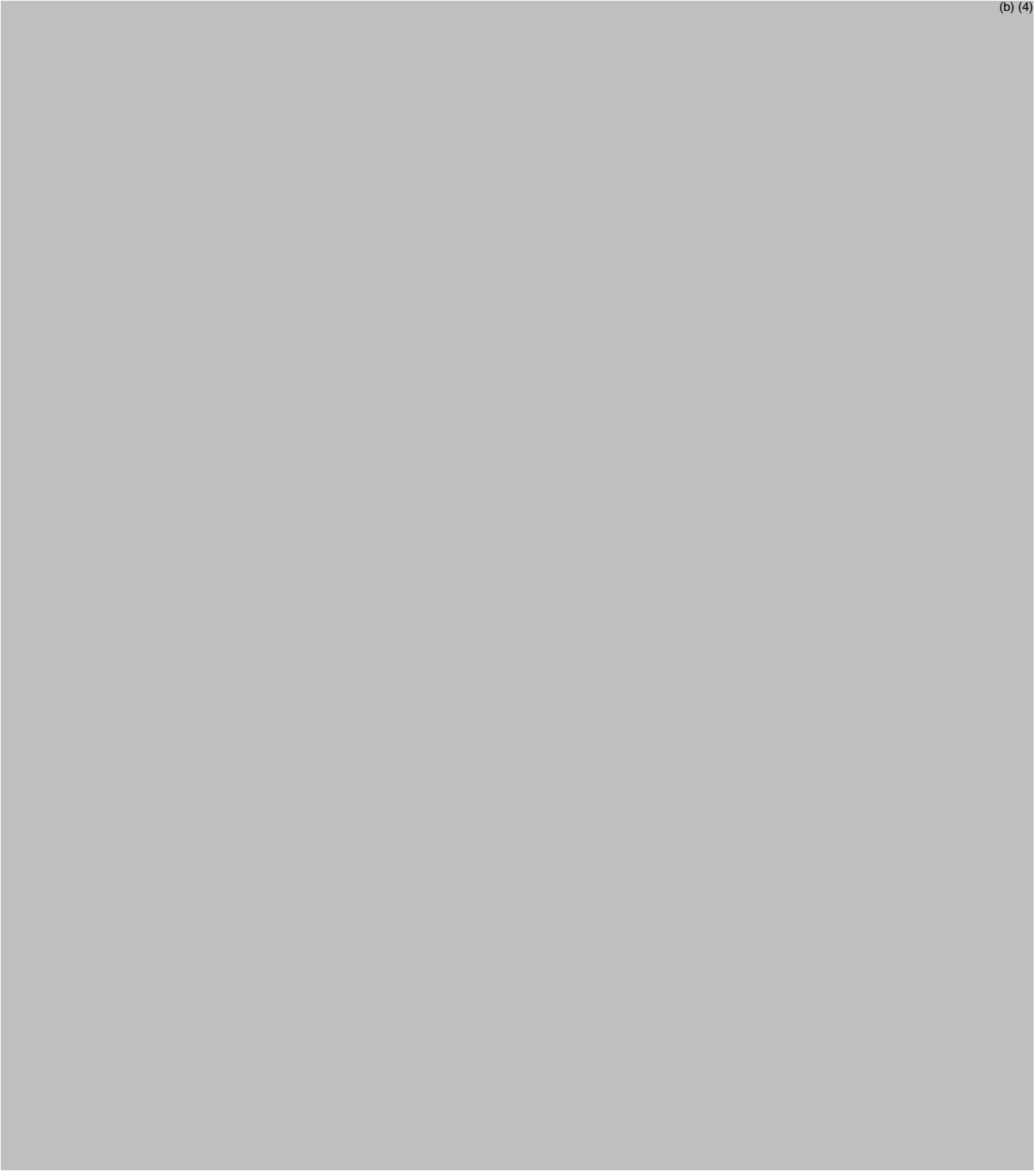


- ii. Outstanding review issues/residual risk: None
- iii. Future inspection points to consider: PoAI recommended for Patheon (b) (4)

b. Drug Product

- i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category



- ii. Outstanding review issues/residual risk: The sponsor has committed to provide the remaining results of the final DS PPQ batch and final DS PPQ validation report in a BLA supplement. This arrangement was agreed to in a pre-BLA meeting with the Agency. Ranges for process parameters, existing protocols, and supportive data should be considered in light of the final PPQ report.

- iii. Future inspection points to consider: PoAI recommended for Patheon Manufacturing Services LLC, Greenville, NC (FEI 1018495)

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/source material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non-Primate Mammalian Cell Substrate/source material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal source		X	
9.	Transgenic Plant source		X	
10.	New Molecular Entity	X		
11.	PEPFAR drug		X	
12.	PET drug		X	
13.	Sterile Drug Product	X		
14.	Other: [fill in information]		X	
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]		X	
16.	Comparability Protocol(s)		X	
17.	End of Phase II/Pre-NDA Agreements		X	
18.	SPOTS (special products on-line tracking system)		X	
19.	USAN assigned name	X		
20.	Other [fill in]		X	
Quality Considerations				
21.	Drug Substance Overage		X	
22.	Design Space	Formulation		X
23.		Process		X
24.		Analytical Methods		X
25.		Other		X
26.	Other QbD Elements		X	
27.	Real Time release testing (RTRT)		X	
28.	Parametric release in lieu of Sterility testing		X	
29.	Alternative Microbiological test methods		X	
30.	Process Analytical Technology in Commercial Production		X	
31.	Non-compendial analytical procedures	Drug Product	X	
32.		Excipients		X
33.		Drug Substance	X	
34.	Excipients	Human or Animal Origin		X
35.		Novel		X
36.	Nanomaterials		X	
37.	Genotoxic Impurities or Structural Alerts		X	
38.	Continuous Manufacturing		X	
39.	Use of Models for Release		X	
40.	Other {fill-in}	X		
	The sponsor obtained agreement to perform a rolling submission of BLA components, including a sequential approach to process validation. The sponsor submitted the first DS PPQ batch information with the original submission, the second DS PPQ batch prior to the midcycle and has committed to provide the final DS PPQ batch in post-approval submission along with the final DS validation report.			

APPEARS THIS WAY ON ORIGINAL



Brian
Roelofs

Digitally signed by Brian Roelofs
Date: 10/07/2020 06:36:59PM
GUID: 57f29d150070ca84f102970a51133e31



William
Hallett

Digitally signed by William Hallett
Date: 10/07/2020 08:58:44PM
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BLA STN 761171

Danyelza (naxitamab)

Y-mAbs Therapeutics, Inc.

Ian McWilliams, PhD, Primary Product Quality Assessor
Brian Roelofs, PhD, Application Technical Lead
Division of Biotechnology Research and Review II
Office of Biotechnology Products

OBP CMC Review Data Sheet

1. BLA#: 761171
2. Review Date: September 30th, 2020
3. Primary Review Team:
 1. Medical Officer: Harpreet Singh (OND/OOD/DOII)
 - a. Clinical OND/OOD
 - i. Primary: Diana Bradford
 - ii. Secondary: Suzanne Demko
 2. Pharm/Tox:
 - a. OND/OOD
 - i. Primary: Stephanie Aungst
 - ii. Secondary: Whitney Helms
 3. Product Quality Team:
 - a. OPQ/OBP:
 - i. Drug Substance (DS)/ Drug Product (DP) Primary Reviewer: Ian McWilliams
 - ii. DS/DP Secondary Reviewer: Brian Roelofs
 - iii. DS/DP Tertiary Reviewer: William Hallett
 - iv. Labeling Reviewer: Vicky Borders-Hemphill
 - b. OPQ/OPMA:
 - i. DS Micro/Facility Reviewer: Viviana Matta
 - ii. DP Micro/Facility Reviewer: Yun Wu
 - iii. DS Micro TL: Max Van Tassell
 - iv. DP Micro TL: Virginia Carroll
 - v. DS/DP Facility TL: Peter Qiu
 - c. Application Technical Lead: Brian Roelofs
 - d. RBPM: Anika Lalmansingh
 4. Clinical Pharmacology:
 - a. OTS/OCP
 - i. Primary: Catharine Bulik
 - ii. Secondary: Hong Zhao
 5. Statistics:
 - a. OTS/OB/DBV
 - i. Primary: Xiaoxue Li
 - ii. Secondary: Pallavi Mishra-Kalyani
 6. OND RPM:
 - a. OND/ORO/DROOD
 - i. Primary: Rebecca Cohen
 - ii. Secondary: Mimi Biable/ Anuja Patel
 7. Labeling
 - a. OND/OOD
 - i. Primary: Bill Pierce
4. Major GRMP Deadlines:
 1. Filing internal meeting: May 5th, 2020
 2. Filing action letter: May 30th, 2020

3. Mid-cycle internal meeting: June 30th, 2020
4. Mid-cycle Sponsor meeting: July 21st, 2020
5. Late-cycle internal meeting: September 21st, 2020
6. GRMP Date: September 30th, 2020
7. Primary review due: October 7th, 2020
8. Secondary review due: October 7th, 2020
9. Late-cycle Sponsor meeting: (tentative) October 13th, 2020
10. Wrap-up meeting: (tentative) October 13th, 2020
11. CDTL memo due: October 14th, 2020
12. PDUFA action date: October 30th, 2020

5. Communications with Sponsor and OND:

Communication / Document:	Date		Submission (Received)	Review Status
	Sent	Received		
Rolling Submission: Module 3 Part 1	-	11/27/2019	eCTD 0001/SDN 1	Complete
Rolling Submission: Module 3 Part 2	-	3/13/2020	eCTD 0003/SDN 3	Complete
Original BLA Submission	-	3/31/2020	eCTD 0004/SDN 4	Complete
Product Quality (PQ) Information Request (IR) 1	4/24/2020	5/1/2020	eCTD 0007/SDN 7	Complete
Rolling Submission: Module 3 Part 3	-	5/7/2020	eCTD 0008/SDN 8	Complete
Response to AOM Meeting Discussion and PQ IR-2	5/4/2020	5/7/2020	eCTD 0009/SDN 9	Complete
Rolling Submission: Module 3 Part 4	-	5/27/2020	eCTD 0013/SDN 13	Complete
Filing Review Memo	5/28/2020		-	Complete
PQ IR 4	6/2/2020	6/12/2020	eCTD 0021/SDN 21	Complete
PQ IR 6	6/5/2020	6/19/2020	eCTD 0024/SDN 24	Complete
Follow up to Rolling Submission: Module 3 Part 4	-	6/25/2020	eCTD 0025/SDN 25	Complete
PQ IR 7	6/18/2020	6/26/2020	eCTD 0026/SDN 26	Complete
PQ IR 8	6/18/2020	7/9/2020	eCTD 0033/SDN 33	Complete
Update to Module 3	-	7/10/2020	eCTD 0034/SDN 34	Complete
PQ IR 9	7/2/2020	7/17/2020	eCTD 0035/SDN 35	Complete
Response to Midcycle T-con 1	8/4/2020	8/4/2020	eCTD 0042/SDN 42	Complete
PQ IR 12	8/13/2020	8/20/2020	eCTD 0050/SDN 50	Complete
PQ IR 13	8/21/2020	8/25/2020	eCTD 0053/SDN 53	Complete
Clinical IR concerning Immunogenicity	8/25/2020	8/26/2020	eCTD 0054/SDN 54	Complete
PQ IR 14	8/25/2020	9/9/2020	eCTD 0060/SDN 60	Complete
PQ IR 16	9/3/2020	9/9/2020	eCTD 0060/SDN 60	Complete
PQ IR 17	9/11/2020	9/15/2020	eCTD 0062/SDN 62	Complete
PQ IR 18	9/15/2020	9/18/2020	eCTD 0064/SDN 64	Complete

6. Drug Product Name/Code/Type:
 - a. Proprietary Name: Danyelza
 - b. Trade Name: Danyelza
 - c. Non-Proprietary Name/USAN: naxitamab
 - d. CAS Registry Number: 1879925-92-4
 - e. Common Name: naxitamab-XXXX (DMEPA review of the 4-letter suffix is ongoing)
 - f. INN Name: naxitamab
 - g. OBP systematic name: MAB HUMANIZED (IGG1) ANTI 6450346 (GANGLIOSIDE GD2) [HU3F8]
 - h. Other names: hu3F8, humanized 3F8

7. Pharmacological Category: Naxitamab-XXXX is a glycolipid disialoganglioside (GD2) binding recombinant humanized monoclonal IgG1 antibody

8. Dosage Form: Injection

9. Strength/Potency: 4 mg/mL in a 10 mL vial, total of 40 mg/vial

10. Route of Administration: IV infusion
 - a. Usual dose: 3 mg/kg per day, infused on Days 1, 3, and 5 per cycle. Up to 5 cycles.

11. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
		(b) (4)	LoA provided May 1 st , 2020 (eCTD 0007/SDN-7)	All DMF's are 'Active'. No review was required as all information related to safety and compatibility with the DS and DP was provided in the BLA.
			LoA provided May 1 st , 2020 (eCTD 0007/SDN-7)	
			LoA provided May 1 st , 2020 (eCTD 0007/SDN-7)	
			LoA provided May 27 th , 2020 (eCTD 0013/SDN-13)	

12. Inspectional Activities:

DS facility: Patheon (b) (4)

- a. 704(a)(4) inspection was completed. From the Office of Biotechnology Product's perspective the facility is acceptable and we recommend a post approval inspection (PoAI). At the time of the completion of this review, OPMA's assessment is ongoing.

DP facility: Patheon Manufacturing Services LLC, 5900 Martin Luther King Jr. HWY, Greenville, NC 27834, USA (FEI: 1018495; DUNS: 079415560)

- a. PLI conducted 08/10/2020-08/14/2020 with a VAI outcome. The compliance review has been finalized with recommendation of approval and concurrence with the VAI determination. PoAI recommended by OPMA.

13. Consults Requested by OBP:
No consults have been requested.

14. Quality by Design Elements:

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

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

15. Precedents:

- a. Unituxin (dinutuximab) – BLA 125516 – anti-human-GD2 monoclonal antibody that bind to GD2+ cells and induces cell death by Fc mediated pathways including antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

16. Administrative: Signature block

Name and Title	Signature and Date
Brian Roelofs, Ph.D. Application Technical Lead, DBRRII/OBP/OPQ/CDER	See electronic signature and date
Ian McWilliams, Ph.D. Primary Reviewer, DBRRII/OBP/OPQ/CDER	See electronic signature and date

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation

The final recommendation for approvability is pending the submission of the completed DS PPQ4 submission material. An addendum will be filed to this review with the final recommendation.

II. List of Deficiencies to be Communicated: No deficiencies.

III. List of Post-Marketing Commitments/Requirements

PMC	Description	Commitment timeline
PMC XXXX	Conduct an analysis of the clonality of the naxitamab master cell bank using a suitable method such as “Next Generation Sequencing”.	by April 2021
PMC XXXX	Perform an additional in-use compatibility study with the specific purpose of testing aggregation and particulates. Samples from the in-use study will also be tested for visible particles and subvisible particles	Date of Study: May 2021 Date of Report: Annual Report covering May 2021

IV. Review of Common Technical Document- Quality Module 1
A. Environmental Assessment of Claim of Categorical Exclusion

Y-mAbs Therapeutics, Inc. is requesting a categorical exclusion from preparing an Environmental Assessment on the basis of 21 CFR 25.31(c) as the production of DANYELZA (naxitamab) is not anticipated to significantly alter the concentration or distribution of substances which occur naturally in the environment, their metabolites, or degradation products in the environment (BLA section 1.12.14).

V. Primary Container Labeling Review
The carton and container labels are reviewed by OBP. The OBP carton and container labeling review will be uploaded as a separate file in Panorama. Assessment will be performed by Dr. Vicky Borders-Hemphill.

VI. Review of Common Technical Document
Quality Module 3.2 and Module 2.3 Quality Overall Summary: The review of Modules 2.3 and 3.2 is included in this review memorandum.

VII. Review of Immunogenicity Assays
Module 5.3.1.4: The review of modules 5.3.1.4 is included in this review memorandum.

BLA EDR Location: <\\CDSESUB5\evsprod\BLA761171\761171.enx>

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Description of Drug Substance and Drug Product

Danyelza (naxitamab) is an anti-GD2 humanized IgG1 monoclonal antibody (hu3F8) that uses the mouse 3F8 (mu3F8) complimentary determination region (CDR) for GD2 specificity. GD2 is a disialoganglioside that is highly expressed on neuroectodermal cancers such as neuroblastoma, melanoma, small-cell lung cancer, and sarcomas, with highly restricted expression on normal tissues including neurons, skin cells, and pain fibers. Neuroblastoma is a childhood cancer that arises from transformed neuroblasts and the GD2 expression on the neuroblastoma cell surface can serve as a selective target for immunotherapy. Naxitamab administered in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) is indicated for neuroblastoma treatment. The binding of naxitamab to GD2+ cancerous neuroblastoma cells triggers antibody-dependent cellular cytotoxicity (ADCC; induced by binding to FcγRIIIa (CD16A)), antibody-dependent cellular phagocytosis (ADCP; binding to Fcγ receptors including CD16A and FcγRIIa (CD32A)) and complement-dependent cytotoxicity (CDC; binding to C1q) resulting in cell death. Naxitamab is not a first in class drug. Unituxin (dinutuximab; BLA 125516) also targets GD2, is indicated for neuroblastoma treatment, and kills targeted GD2+ neuroblastoma cells by ADCC and CDC mechanisms.

Assessor comments: The Figures and Tables in the assessment were directly copied from the original BLA submission and subsequent BLA amendments during the review cycle unless otherwise noted. The assessor’s comments are provided in blue italics.

P: DRUG PRODUCT

3.2.P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Naxitamab drug product (DP) is provided as an aqueous solution in a single-dose 10 mL vial at 4 mg/mL. The composition of the finished naxitamab DP is summarized in the table below.

Ingredients	Component	Quantity		Function	Reference to the Standards
		Per mL	Per 10 mL		
Drug substance	Naxitamab	4 mg	40 mg	Active substance (b) (4)	In-house RS
Excipients	(b) (4)	6.26 mg	62.6 mg		Ph. Eur., BP, USP, JP, E331 suitable for use as excipient.
	Citric acid anhydrous	0.71 mg	7.1 mg		
	Sodium chloride	7.01 mg	70.1 mg		
	Poloxamer 188	1.5 mg	15 mg		
	(b) (4)			Ph. Eur., USP	
	WFI	q.s. to 1 mL	q.s. to 10 mL		

Assessor comments: *No novel excipients are used in naxitamab DP formulation. The final formulation contains sodium citrate (b) (4) Sodium chloride is added (b) (4) Poloxamer 188 is added (b) (4) There are no concerns with the composition of naxitamab DP. See section [3.2.P.2 Batch Formula](#) for more excipient information.*

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

3.2.P.8 STABILITY

3.2.P.8.1 Stability Summary and Conclusion

The originally proposed storage shelf-life for naxitamab DP under long term conditions ($5^{\circ}\text{C} \pm 3^{\circ}\text{C}$) was (b) (4)

(b) (4) The proposed $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ long term storage DP shelf-life is based on data accumulated from the following stability studies in the table below. For $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ long term storage studies samples are tested at 0, 3, 6, 9, 12, and 24 months and $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ accelerated storage studies are tested at 0, 1, 2, and 3 months.

Table 3.2.P.8.1-1 Available naxitamab Drug Product Stability Data

Drug Product Batch	Long-term -70°C ± 10°C	Long-term -20°C ± 5°C	Long-term 5°C ± 3°C	Accelerated 25°C ± 2°C	Freeze-thaw	Status
PHB2011A	60 months	60 months	Not tested	Not tested	9 cycles	Completed
PHB2011B	60 months	60 months	Not tested	Not tested	9 cycles	Completed
PHB2011C	60 months	60 months	Not tested	Not tested	9 cycles	Completed
AF9843	Not tested	24 months ^a	12 months	3 months	Not tested	Ongoing
AJ9755	Not tested	18 months	12 months	3 months	Not tested	Ongoing
AK2183	Not tested	18 months	24 months	3 months	Not tested	Ongoing
AL0362	Not tested	12 months	12 months	3 months	Not tested	Completed
AL3308	Not tested	12 months	12 months	Not tested	Not tested	Ongoing
AM2042 (PPQ#1)	Not tested	3 months	6 months	Not tested	Not tested	Ongoing
AM6337 (PPQ#2)	Not tested	Not tested	0 months	Not tested	Not tested	Ongoing
AN0267 (PPQ#3)	Not tested	Not tested	0 months	Not tested	Not tested	Ongoing

a T=0 was 11 months after the date of manufacturing (b) (4)

Assessor comment: (b) (4)

Subsequently, the longest storage period of data provided for naxitamab DP under the proposed long-term storage condition is 12 months of real time data (assessed below in section 3.2.P.8.3). The proposed (b) (4) shelf life is not supported with real-time data and is not in line with ICH 5QC guidelines. This was communicated to the Sponsor and they accepted a 12-month shelf-life under long-term storage conditions in the IR response received September 9th, 2020 (eCTD 0060/SDN-60).

3.2.P.8.2 Post-Approval Stability Commitment

The proposed post-approval stability program for future manufacture of naxitamab DP is provided in the following table:

Table 3.2.P.8.2-2 Post-Approval Stability Protocol for naxitamab Drug Product at Long-term Conditions in Upright and Inverted Position (5°C ± 3°C)

Test	Shelf-life Specification	Time Point (Months)							
		0	3	6	9	12	18	24	36
Clarity (Ph. Eur. 2.2.1, USP <1>)	(b) (4)	TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
Color (Ph. Eur. 2.2.2, USP <1>)		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
Visible particles (USP <790>)		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
pH (Ph. Eur. 2.2.3, USP <791>)		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
Osmolality (Ph. Eur. 2.2.35, USP <785>)		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
OD280 (WV00944)		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
GD2 ELISA (WV01031)		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
ADCP (BAG/M046)		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
CDC (BAG/M047)		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
Biacore CD16 (016853GMP.BUK)		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR

Test	Shelf-life Specification	Time Point (Months)							
		0	3	6	9	12	18	24	36
SE-UPLC (WV00944)	(b) (4)	TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
Non-reducing CE-SDS (WV01109)		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
Reducing CE-SDS (WV01109)		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
cIEF (WV01110)		TBR	TBR	TBR	TBR	TBR	TBR	TBR	TBR
Endotoxin (LAL) (Ph. Eur. 2.6.14 Method D, USP <85>)		TBR	NT	NT	NT	TBR	NT	TBR	TBR
Container closure integrity (Helium leak test, Selbly- 12)		NT	NT	NT	NT	TBR	NT	TBR	TBR
Particulate matter (USP <788> Method 2)		TBR	NT	NT	NT	TBR	NT	TBR	TBR
		TBR	NT	NT	NT	TBR	NT	TBR	TBR
Leachables ^a		TBD	TBD	TBD	TBD	TBD	TBD	TBD	TBD

ADCP = antibody-dependent cellular phagocytosis; CDC = complement-dependent cytotoxicity; CE-SDS = capillary electrophoresis sodium dodecyl sulfate; cIEF = capillary isoelectric focusing; ELISA = enzyme-linked immunosorbent assay; EU = endotoxin units; GD2 = disialoganglioside 2; HC = heavy chain; IgG = immunoglobulin G; LC = light chain; NT = not tested; OD280 = optical density at 280 nm; Ph. Eur. = European Pharmacopoeia; SE-UPLC = size-exclusion ultra-performance liquid chromatography; TBD = To be decided, according to protocol to be finalized no later than December 2020; TBR = to be reported; USP = United States Pharmacopoeia.

^a Testing for leachables will be performed for one commercial batch.

Assessor comments:

(b) (4)

In the IR response, provided September 9th, 2020 (eCTD 0060/SDN-60) the stability testing frequency was updated for future commercial manufacturing stability lots and is reflected in the table above. One naxitamab post approval drug product batch per year will be placed on stability according to the protocol described in the table above. Stability samples will be stored in upright and inverted positions for newly manufactured DP lots moving forward. Samples will also be tested using updated cIEF acceptance criteria with appropriate control ranges.

A commitment to complete PPQ1, PPQ2, and PPQ3 DP stability studies including ADCP, CDC, and Biacore CD16 methods and the updated stability testing frequency was provided in the September 9th, 2020 (eCTD 0060/SDN-60) IR. Samples will also be tested using updated cIEF acceptance criteria with appropriate control ranges. Stability studies with the three DP PPQ lots are currently ongoing. All PPQ stability vials were stored in an inverted position and due to lack of available samples, no data will be available from naxitamab DP PPQ lots stored under long-term conditions in upright positions.

The provided updates to the stability program testing, inverted and upright stability sampling, and testing frequency for the future commercial manufacturing stability DP lots and DP PPQ lots are acceptable.

A commitment to perform leachables on two PPQ DP lots (PPQ#1 (AM2042) and PPQ#2 (AM6337)) and one future commercial DP lot is provided (09/08/2020; eCTD 0060/SDN-60). Leachable samples will be available from inverted stability samples, which represents worst case conditions due to contact time with the stopper. This commitment and planned sampling of inverted stability samples is acceptable. (b) (4)

3.2.P.8.3 Stability Data:

The stability data was provided in an IR response submitted August 25th, 2020 (eCTD 0053/SDN-53) and September 9th, 2020 (eCTD 0060/SDN-60). DP lot AJ9755 is made from MSK DS that was reformulated to the to-be-marketed formulation; this lot represents MSK material under the to-be-marketed formulation. The remaining DP lots are made from DS from the to-be-marketed manufacturing process and formulation. The stability data for the proposed long-term storage condition, 5°C ± 3°C, are summarized in the table below.

Test	Acceptance criteria	5°C ± 3°C DP stability data (Time 0 – X month)						
		AJ9755	AK2183	AL0362	AL3308	AM2042 (PPQ1)	AM6337 (PPQ2)	AN0267 (PPQ3)
Clarity	(b) (4)	Clear (0) – clear (12)	Ref I (0) – < Ref I (12)	Clear (0) – < Ref I (12)	Clear (0) – Ref I (12)	< Ref III (0) – < Ref I (6)	< Ref II (0) – TBR (3)	< Ref I (0) – TBR (3)
Color	(b) (4)	colorless (0) – colorless (12)	< B9 (0) – < B9 (12)	< B9 (0) – < B9 (12)	< B9 (0) – < B9 (12)	Conforms (0 – 6)	Conforms (0) – TBR (3)	< BY5 (0) – TBR (3)
pH	(b) (4)	5.7 (0) – 5.8 (12)	5.7 (0) – 5.8 (12)	5.7 (0) – 5.8 (12)	5.7 (0) – 5.8 (12)	5.7 (0) – 5.7 (6)	5.8 (0) – TBR (3)	5.7 (0) – TBR (3)
Osmolality	(b) (4)	289 (0) – 289 (12)	290 (0) – 290 (12)	289 (0) – 290 (12)	290 (0) – 290 (12)	289 (0) – 287 (6)	290 (0) – TBR (3)	290 (0) – TBR (3)
OD280	(b) (4)	4.2 (0) – 4.1 (12)	4.2 (0) – 4.3 (12)	4.0 (0) – 4.0 (12)	4.3 (0) – 4.2 (12)	4.0 (0) – 4.1 (6)	4.0 (0) – TBR (3)	4.0 (0) – TBR (3)

GD2 ELISA	(b) (4)	122 (0) – 117 (12)	113 (0) – 92 (12)	112 (0) – 87 (12)	99 (0) – 105 (12)	101 (0) – 93 (6)	92 (0) – TBR (3)	97 (0) – TBR (3)
		Not tested	Not tested	Not tested	Not tested	Conforms (0 – 6)	Conforms (0) – TBR (3)	Conforms (0) – TBR (3)
ADCP		Not tested	Not tested	Not tested	92 (0) – 101 (12)	100 (0) – 97 (6)	92 (0) – TBR (3)	99 (0) – TBR (3)
CDC		Not tested	Not tested	Not tested	74 (0) – 93 (12)	90 (0) – 93 (6)	108 (0) – TBR (3)	97 (0) – TBR (3)
Biacore CD16		Not tested	Not tested	Not tested	Not tested	66 (0) – 96 (6)	79 (0) – TBR (3)	82 (0) – TBR (3)
SE-UPLC		98 (0) – 98 (12)	97 (0) – 96 (12)	96 (0) – 98 (12)	98 (0) – 97 (12)	97 (0) – 97 (6)	98 (0) – TBR (3)	98 (0) – TBR (3)
Non-reducing CE-SDS		99.0 (0) – 99.1 (12)	98.7 (0) – 97.9 (12)	99.7 (0) – 98.3 (12)	98.7 ^a (0) – 98.5 (12)	98 (0) – 99 (6)	99 (0) – TBR (3)	99 (0) – TBR (3)
Reducing CE-SDS		98.8 (0) – 98.9 (12)	98.9 (0) – 98.8 (12)	98.9 (0) – 98.8 (12)	97.6 ^a (0) – 98.5 (12)	99 (0) – 98 (6)	97 (0) – TBR (3)	99 (0) – TBR (3)
cIEF		Not tested	Not tested	Not tested	Conforms (0 – 12)	21.6 (0) – 22.2 (6)	TBR (0) – TBR (3)	TBR (0) – TBR (3)
	37.4 (0) – 36.3 (6)					TBR (0) – TBR (3)	TBR (0) – TBR (3)	
	40.9 (0) – 41.5 (6)					TBR (0) – TBR (3)	TBR (0) – TBR (3)	
Endotoxin		Not tested	Not tested	Not tested	Not tested	< 1 EU/mg (0) – TBR (12)	< 1 EU/mg (0) – TBR (12)	< 0.1 EU/mg (0) – TBR (12)
CCI		Not tested	Not tested	Not tested	Not tested	TBR (12)	TBR (12)	Conforms (0) – TBR (12)
Particulate matter		Not tested	Not tested	Not tested	5 (0) – 17 (12)	2 (0) – TBR (12)	11 (0) – TBR (12)	3 (0) – TBR (12)
Particulate matter		Not tested	Not tested	Not tested	2 (0) – 10 (12)	1 (0) – TBR (12)	7 (0) – TBR (12)	1 (0) – TBR (12)

Footnote a: "Calculated as the average of two results."

TBR: To be reported.

Assessor comments: *There are no significant trends in the stability data provided for naxitamab stored under the long-term storage condition (5°C ± 3°C) up to 12 months or under accelerated conditions up to 3 months (not replicated in this review). Of note, the only minor stability trend noted was an increase in HMW impurities with the originally proposed long-term storage condition of (b) (4) the Sponsor changed the long-term storage condition to 5°C ± 3°C after this stability trend was noted.*

The stability data provided for AJ9755, AK2183, AL0362, and AL3308 support up to 12 months under 5°C ± 3°C long-term storage conditions. The Sponsor proposes (b) (4) of storage under long-term conditions, but this is not supported with real time data (b) (4) GD2 binding by ELISA demonstrates consistent binding out to 12 months of storage for the DP lots. Potency data for ADCP and CDC are provided for DP lot AL3308 out to 12 months and is consistent under long-term storage conditions. There is concern that (b) (4) will lead to an overall reduction in GD2 binding capacity of the antibody over time, but there is no trend in overall reduction of GD2 binding to 12 months. Further, there is concern that (b) (4) will reduce Fc binding ability, but there is no trend in overall reduction in Fc mediated functions (ADCP and CDC) out to 12 months. The data provided support storage of naxitamab for 12 months under long-term

storage conditions. The stability testing program ensure long-term product quality by assessing identity, purity, and potency. The Sponsor plans to provide additional stability data to support longer shelf lives in future submissions.

After analysis of the provided DP batch release data, (b) (4)

(b) (4) As mentioned previously, based on our analysis, there are no stability trends noted with naxitamab stored under the long-term storage condition (5°C ± 3°C) up to 12 months. Further, no data is trending (b) (4) As the stability of naxitamab DP is stable out to 12 months with no discernable trend, (b) (4) will not impact product quality or product safety.

The Sponsor plans to re-evaluate release specifications after 15 DS and DP lots are manufactured, and plans to perform stability studies to the (b) (4) As more data becomes available, the evaluation of stability indicating properties and appropriate stability specifications will become clearer for discussions (b) (4)

The Sponsor has identified several stability indicating properties of naxitamab, which are discussed under DS section [3.2.S.7.3 Stability Data](#).

Assessor comments: Because the DP has (b) (4)

3.2.A APPENDICES TABLE OF CONTENTS

3.2.A.1 FACILITIES AND EQUIPMENT

Assessor comments: This section is deferred to the OPMA review team.

3.2.A.2 ADVENTITIOUS AGENTS SAFETY EVALUATION

Assessor comments: See discussion under [3.2.S.2.3 Control of Materials](#).

3.2.A.3 NOVEL EXCIPIENTS

There are no excipients of human or animal origin. There are no novel or non-compendial excipients.

Assessor comments: See discussion under [3.2.P.1 Description and Composition of the Drug Products](#).

3.2.R REGIONAL INFORMATION (USA)

Assessor comments: In the document 3.2.R Regional Information section the Sponsor provided the following:

1. Executed production protocols from manufacturing of drug substance batch 1912-074 and drug product batch AM2042.
2. Post submission commitments for finalization of validation studies.

3.2.R.1 EXECUTED BATCH RECORDS

Assessor comments: *The provided batch records for DS batch 1912-074 and DP lot AM2042 were assessed and the relevant information was incorporated in sections 3.2.S.2.6 and 3.2.P.2.3, respectively.*

3.2.R.2 METHOD VALIDATION PACKAGE

Assessor comments: *All analytical method material is reviewed under [3.2.S.4.2 Analytical Procedures](#) and [3.2.S.4.3 Validation of Analytical Procedures](#).*

3.2.R.3 COMPARABILITY PROTOCOLS

Assessor comments: *No comparability protocols were provided with the submission.*

5.3.1.4 REPORTS OF BIOANALYTICAL AND ANALYTICAL METHODS FOR HUMAN STUDIES

ADA Immunogenicity Assay Background

Clinical studies 11-009, 12-116, 12-230, and retrospective 2PR01 used partially-validated immunogenicity ELISA assays "(b) (4) -SOP-RD-001.01" and "MSKCC-SOP-173" to assess the development of anti-drug antibodies (ADA). For the pivotal clinical study (Trial 201) patient samples were analyzed with the validated ADA screening and confirmatory assays described in report VCA23074 "Validation of an ADA Immunoassay for the Detection of anti-hu3F8 Antibodies in Human Serum by Electrochemiluminescence". Positive samples were further analyzed for neutralizing antibodies (NAb) using the validated assay described in report VCA23075 "Validation of an nADA Immunoassay for the Detection of anti-hu3F8 Antibodies in Human Serum by Electrochemiluminescence".

Assessor comment: *The method validation reports for the immunogenicity assays used for clinical studies 11-009, 12-116, 12-230, and retrospective 2PR01 were not provided with the BLA submission package. An IR was sent to the Sponsor from Clinical Pharmacology reviewers but the validation reports were not provided in the response. Additionally, an IR was sent with the Clinical review team to clarify which immunogenicity assay was used for pre-screening to identify ADA-positive patients for trials 12-230 and 201. The Sponsor's response received on August 26th, 2020 in eCTD 0054/SDN-54 'Response to 24 August 2020 RFI' provided Table 1.11.3-2 that clarified that the partially validated immunogenicity assays were used to pre-screen individuals from trial 12-230, and the validated ADA assay (VCA23074) and NAb assay (VCA23075) were used to pre-screen individuals in Trial 201. Subsequently, ADA assessment will rely on the validated ADA assay, VCA23074, for screening and confirmation of ADA development in clinical study 201. Additionally, the validated NAb assay, VCA23075, will be used to assess the formation of NAb in clinical study 201.*

Validation of Anti-Drug Antibody (ADA) Assay

The validated ADA assay, VCA23074, is performed using a Meso Scale Diagnostics (MSD) electrochemiluminescence (ECL) based immunoassay in bridging format. Briefly, study samples are diluted 1:20 with aqueous acetic acid and incubated on an ECL plate with Biotin-hu3F8 (conjugate for capturing) and Sulfo-hu3F8 conjugate (detection). If there are ADA present, these antibodies will act as a bridge of the plate bound biotin antibodies to the free floating sulfo-tagged antibodies. ADA complexes are quantified by fluorescence. The results of ADA assay validation are provided in Table 1.

Table 1: Validation Results and Assessor Analysis for ADA assay VCA23074 used in Study 201

Validation Parameter	Validation Report: VCA23074	Assessor Comment
Contract Research Org	(b) (4)	<i>The CRO is acceptable.</i>

Assay principle	MSD ECL – bridging format Biotin-hu3F8 from (b) (4) (batch# B-18175A) Sulfo-hu3F8 from (b) (4) (batch# S-18304A, S-18175B)	<i>MSD ECL is a common ADA assay format. The antibodies used for bridging are hu3F8, which is another name for naxitamab. The assay format is acceptable for anti-naxitamab ADA determination.</i>
Sample Pretreatment (Acid dissociation)	Acid dissociation with acetic acid (1:20 dilution initial step).	<i>Acetic acid is commonly used for acid dissociation. The report states that the acid dissociation step is performed with a 1:20 dilution. The final MRD is 1:53, which accounts for further sample dilution after the acid dissociation step. The 2019 immunogenicity guidance states that an MRD up to 1:100 is acceptable; subsequently, the proposed acid dissociation step aligns with the 2019 guidance.</i>
Positive control (PC)	anti-mAb hu3F8 F(ab)2; Rabbit, affinity purified rabbit serum; (b) (4) batch# (b) (4) 8AK03210	<i>The PC is an affinity purified anti-naxitamab antibody. This antibody was derived in rabbit and is likely polyclonal, though it is not clarified. It is detectable in the bridging format. This is acceptable for use in the ADA assay.</i>
PC Dose Curve and Hook Effect	No PC curve provided.	<i>No PC curve is provided. However, the LPC, MPC, and HPC provide clear low, medium, and high RLU values when used in the assay (Table 4 of validation report) that demonstrate that these values are suitable for purpose. Additionally, sensitivity analysis was performed using a range up to 100 ng/mL and did not show hook effects at these levels when sensitivity is critical. The selection and use of the LPC, MPC, and HPC are acceptable for use in the ADA assay.</i>
LPC	14.2 ng/L	
MPC	500 ng/mL	
HPC	2500 ng/mL	
Matrix and NC	Human serum was obtained from (b) (4)	<i>Normal human serum was used to validate the ADA assay. This is acceptable for validation. The cut-points established using normal serum need to be confirmed with in-study data. The established cut-points using normal human sera appear appropriate and are discussed in detail in Assessment of Assay Performance in Clinical Studies.</i>
MRD	53-fold 10 µL (screening assay)	<i>The MRD of 1:53 aligns with the 2019 immunogenicity guidance</i>

		<i>recommendations and accounts for the acid dissociation step. Of note, the reported titer assay does not calculate MRD; a titer of 1 will equal 53 when accounting for MRD.</i>
NC system suitability range	0.5 – 2x mean NC Values: 18.8 – 75.2 RLU	<i>The values set for system suitability per run are appropriate. The LPC must be above the plate cut-point in order for the assay to proceed.</i>
LPC system suitability range	uninhibited response ≥ rCP Values: ≥ rCP	
MPC system suitability range	≥ mean response + $t_{0.005,df} \times SD$ Values: ≥ 358.7 RLU	
HPC system suitability range	≥ mean response + $t_{0.005,df} \times SD$ Values: ≥ 2032.3 RLU	
Screening cut-point (SCP) Floating cut-point; [Mean NC response] + [SCP]	5% FPR; SCP = 3.1 Generated from 50 drug naive samples. 6 datasets performed by 2 analysts.	<i>The Sponsor calls the SCP a 'correction factor C' because it is the validation cut-point minus the mean validation NC value. The Sponsor also calls the in-study cut-point the 'run-specific screening cut-point'. The generation of this cut-point was performed appropriately with sufficient samples, runs, analysts, and statistical methods. Confirmation of in-study cut-point is discussed under Assessment of Assay Performance in Clinical Studies.</i>
Confirmatory cut-point (CCP) Fixed cut-point	1% FPR using Robust Parametric Approach; CCP = 21.9%	<i>The Sponsor calls this the 'specificity cut-point' (iCP). Data was generated in parallel with screening runs (in the presence of drug) meaning 50 individual sera, 6 runs, 2 analysts. The generation of this cut-point was performed appropriately with sufficient samples, runs, analysts, and statistical methods.</i>
Titer Cut Point (TCP) Floating cut-point; [Mean NC response] + [TCP]	There is a 5% and 0.1% TCP; 0.1% will be used TCP = 7.4	<i>The Sponsor tested two potential titer cut-points. The 5% is above the recommended FPR recommended in the 2019 immunogenicity guidance. The Sponsor has decided to proceed with the 0.1% FPR titer cut-point, which is consistent with guidance recommendations. The generation of this cut-point was performed appropriately with sufficient samples, runs, analysts, and statistical methods.</i>
Assay Drug tolerance	2000 ng hu3F8/ mL human serum tested at LPC level 14.2 ng/mL	<i>The level of drug tolerance identified for the naxitamab ADA assay is 2000 ng/mL. The establishment of the drug</i>

	<u>Results of drug interference</u> 8000 ng/mL (<rCP, negative) 4000 ng/mL (<rCP, negative) 2000 ng/mL (reactive) 1000 ng/mL (reactive) 500 ng/mL (reactive)	<i>tolerance was performed appropriately with several concentrations of naxitamab. Serum levels of naxitamab at ADA sampling at day 12 of the treatment cycle are above 2000 ng/mL. Naxitamab is likely to interfere at this timepoint; see discussion in Assessment of Assay Performance in Clinical Studies.</i>
Target tolerance	Not performed	<i>The Sponsor does not perform target tolerance in their ADA assay validation. Serum levels of GD2 have been reported in patients with neuroblastoma, which could potentially interfere with the ADA assay. However, the ADA data provided, discussed in Assessment of Assay Performance in Clinical Studies, demonstrates that the ADA assay can detect and confirm ADA positivity in this patient population. Therefore, the risk of target interference is low because of the proven functionality of the ADA assay.</i>
Sensitivity	Screening = 14.1 ng/mL	<i>It is unclear if the 14.1 ng/mL screening sensitivity is calculated after accounting for the 1:53 MRD. If not, the assay sensitivity equals 747.3 ng/mL. Generally, this is above the 2019 immunogenicity criteria of 100 ng/mL or previous guidance of 250 – 500 ng/mL. However, the assay has demonstrated the ability to detect ADA positive samples that have NAb activity (see Assessment of Assay Performance in Clinical Studies), which demonstrates that the sensitivity of the assay is adequate for the patient population.</i>
Repeatability/Intra-assay variability	NC = 2.4% LPC = 5.1% MPC = 3.2% HPC = 7.3%	<i>%CV are less than 20% and are acceptable for ADA assessment.</i>
Intermediate Precision (IP)/inter-assay variability	NC = 18.2% LPC = 14.4% MPC = 14.0% HPC = 15.6%	

Selectivity	Sensitivity: 9/10 confirmed at LPC of 14.2 ng/mL Recovery: 9/10 confirmed at LPC and HPC	<i>Sensitivity: 9/10 individual serum samples were reactive with spiked LPC. The selectivity is acceptable.</i> <i>Recovery: All samples tested were reactive and recovery of 9/10 LPC and 9/10 HPC samples were between 80-120%. This is acceptable.</i>
Stability	15 hours at room temperature 6 freeze/thaw cycles (-20°C/ RT and -80°C/ RT) at least 61 days at -20°C at least 61 days at -80°C Covered range: up to 20.0 µg/mL human serum	<i>Sample stability assessment is appropriate and demonstrates that samples can undergo several freeze/thaw cycles.</i>
Lipemia	Not performed	<i>Lipemia analysis was not performed. However, the ADA data provided, discussed in Assessment of Assay Performance in Clinical Studies, demonstrates that the ADA assay can detect and confirm ADA positivity in the patient population. Therefore, the risk of interference due to lipemia is low.</i>
Hemolysis	No interference noted	<i>The Sponsor notes several clinical samples where hemolysis occurred. They have demonstrated in the validation report that hemolysis will not affect ADA assay function. This is acceptable.</i>
ADA Assay Assessment	Suitable for Intended Purpose	

Validation of Neutralizing Anti-Drug Antibody Assay

The validated NAb assay, VCA23075, is performed using an MSD ECL based immunoassay in direct binding format. Briefly, study samples are diluted 1:10 for acid dissociation. Serum is incubated with biotin-anti-hu3F8 during neutralization to deplete serum naxitamab. The non-bound solution is then transferred to biotin-GD2 coated streptavidin plates, resulting in a final 1:40 MRD. Sulfo-hu3F8 is then added to the plate to bind to the plate-bound GD2 and binding is measured by overall fluorescence. If NAb are present, they will bind to and inhibit the sulfo-hu3F8, resulting in diminished overall fluorescence. The results of the NAb validation study are provided in Table 2.

Table 2: Validation Results and Assessor Analysis for NADA assay used in clinical study 201

Validation Parameter	Clin Study 201 Validation Report: VCA23075 SOP: SM3-430	Assessor Comment
Contract Research Org	(b) (4)	<i>The CRO is acceptable.</i>
Assay principle	ECL-ELISA. Biotin-GD2 coated streptavidin	<i>MSD ECL is a common assay format. The</i>

	plates capture Sulfo-hu3F8. If NAb are present, they will bind to sulfo-hu3F8 and block binding to GD2-biotin coated. This causes a signal decrease proportional to the amount of NAb.	<i>antibodies used are appropriate and the methodology is acceptable.</i>
Sample Pretreatment (Acid dissociation)	1:10 dilution for acid dissociation. After neutralization samples are depleted using biotin-anti-hu3F8. Final sample dilution is 1:40 MRD.	<i>Acid dissociation is described and properly calculated into the MRD.</i>
Positive control (PC)	anti-mAb hu3F8 F(ab) ₂ ; Rabbit, affinity purified rabbit serum; (b) (4) batch# (b) (4) 18AK03210	<i>The PC is an affinity purified anti-naxitamab antibody. This antibody was derived in rabbit and is likely polyclonal, though it is not clarified. It is detectable in the bridging format. This is acceptable for use in the NAb assay.</i>
PC Dose Curve and Hook Effect	PC from sensitivity analysis: 1000 ng/mL to 31.25 ng/mL. No hook effect seen.	<i>Table 3 of the NAb validation report (VCA23075) provides the values of the provisional LPC at 200 ng/mL, MPC at 400 ng/ml, and HPC at 800 ng/ml. Due to low sensitivity at 200 ng/mL the Sponsor selected 400 ng/ml as the LPC. The values in Table 3 show clear inhibition of signal with increasing concentration of positive control. The selection and use of the LPC at 400 ng/mL and HPC at 800 ng/mL are reasonable. There is only a 2-fold difference between the chosen LPC and HPC, which means that the detection range for the NAb assay is reduced. The NAb detection demonstrated the ability to identify positive and negative NAb individuals (see Assessment of Assay Performance in Clinical Studies). Taken together, the range of positive controls is adequate for the validation of the NAb assay.</i>
LPC	400 ng/mL	
HPC	800 ng/mL	
Matrix and NC	Normal human sera	<i>Normal human serum was used to validate the NAb assay. This is acceptable for validation. The cut-points established using normal serum need to be confirmed with in-study data. The established cut-points using normal human sera appear appropriate and are able to identify NAb+ individuals. See Assessment of Assay Performance in Clinical Studies.</i>

MRD	1:40	<i>MRD dilution accounts for acid dissociation and aligns with the 2019 immunogenicity guidance recommendations.</i>
NC system suitability range	0.5 – (2*mean NC) Values: 7369.5 – 29478 RLU	<i>The values set for system suitability per run are appropriate. The LPC must be above the plate cut-point in order for the assay to proceed.</i>
LPC system suitability range	Response ≤ rCP Values: ≤ rCP (expected to be reactive)	
HPC system suitability range	≤ mean response + $t_{0.005,df} \times SD$ Values: ≤ 7686.3 RLU	
NAb assay cut-point (NACP); floating; [Mean NC response] + [NACP]	1% FPR; NACP = rCP = -2890 Generated from 50 drug naive samples. 6 datasets performed by 2 analysts.	<i>The generation of this cut-point was performed appropriately with sufficient samples, runs, analysts, and statistical methods. Confirmation of in-study cut-point is discussed under Assessment of Assay Performance in Clinical Studies.</i>
Assay Drug tolerance	500 ng of hu3F8 / mL human serum <u>Results of drug interference at LPC (400 ng/mL)</u> 30,000 ng/mL (>rCP, negative) 10,000 ng/mL (>rCP, negative) 3,500 ng/mL (>rCP, negative) 1000 ng/mL (>rCP, negative) 500 ng/mL (reactive) 250 ng/mL (reactive)	<i>The assay drug tolerance is below the expected serum concentration of clinical samples (≥ 500 ng drug/mL of serum; see Assessment of Assay Performance in Clinical Samples), which indicates that assay interference may occur at all proposed sampling timepoint after initial baseline sampling.</i>
Target tolerance	Not performed	<i>The Sponsor does not perform target tolerance testing. Serum levels of GD2 have been reported in patients with neuroblastoma, which could potentially interfere with the NAb assay. As discussed in Assessment of Assay Performance in Clinical Studies, the NAb assay can detect NAb positivity in clinical samples. Therefore, the risk of target interference is low.</i>
Sensitivity	At 90% screening sensitivity, 415 ng/mL Range of PC = 1000 ng/mL to 31.25 ng/mL 2 fold dilution.	<i>Sensitivity assessment was performed appropriately and is acceptable for a NAb assay.</i>
Repeatability/Intra-assay variability	NC = 3.8% LPC (400 ng/mL) = 3.8% HPC (800 ng/mL) = 7.6%	<i>%CV are less than 20% and are acceptable for NAb assessment.</i>
Intermediate Precision (IP)/inter-assay variability	NC = 15.1% LPC (400 ng/mL) = 10.6% HPC (800 ng/mL) = 10.3%	

Selectivity	10/10 confirmed at 400, 600, and 800 ng/mL	<i>The LPC demonstrated 80-120% recovery in 80% of samples. The 600 and 800 ng/mL recovery did not pass with 30% of samples having recovery beyond 80-120%. The Sponsor states that because of the extra steps with acid dissociation and purification, increased variability is expected. However, despite failing the recovery criteria, all 400, 600, and 800 ng/mL samples were reactive in the assay. Subsequently, the reduced recovery does not affect the overall determination of NAb positivity and is acceptable.</i>
Robustness	Recovery at 400 ng/mL PC: 8/10 passed Recovery at 600 ng/mL PC: 3/10 passed Recovery at 800 ng/mL PC: 3/10 passed	
Stability	Tested up to 800 ng/mL in human sera: 36 days at -20°C 36 days at -80°C 7 freeze/thaw cycles (-20°C/RT) 6 freeze/thaw cycles (-80°C/RT)	<i>Sample stability assessment is appropriate and demonstrates that samples can undergo several freeze/thaw cycles.</i>
Lipemia	Not provided	<i>Lipemia analysis was not performed. Lipemia may interfere with the NAb assay, however, no interference is noted with clinical samples where NAb were tested. Although these samples are limited, it demonstrates the functionality of the NAb assay in real world application. Based on these results, the risk of lipemia interference is considered to be low. This is acceptable.</i>
Hemolysis	No interference noted	<i>Testing was performed with hemolysis serum and the LPC. 3/3 samples were reactive under these testing conditions, demonstration that hemolysis does not interfere in the NAb assay.</i>
NADA Assay Assessment	Suitable for Intended Purpose	

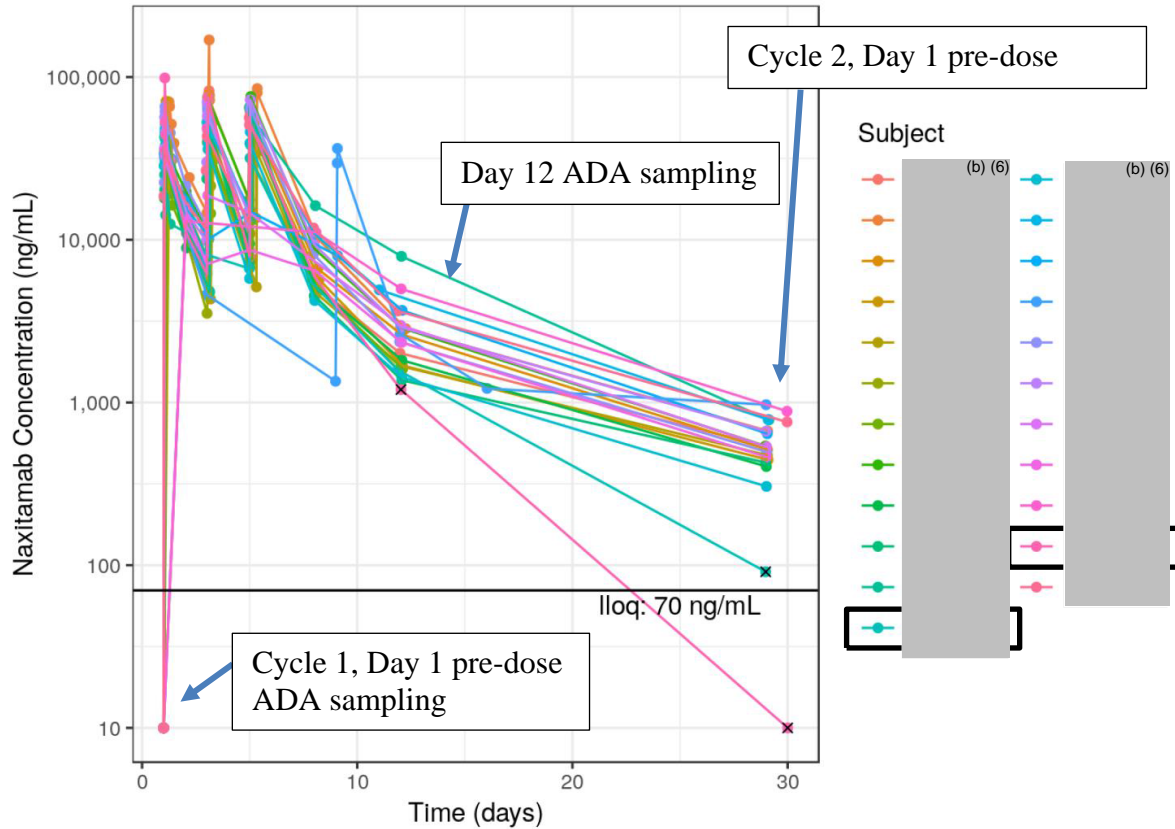
Assessment of Assay Performance in Clinical Studies

Studies of ADA (using the validated assay reported in VCA23074) and NAb (using the validated assay reported in VCA23075) development in clinical study 201 are provided in the following sections:

1. 2.7.2 Summary of Pharmacology Studies
2. 5.3.5.2 ACA23079-02 Interim Report 2 – contains NAb raw data
3. 5.3.5.2 ACA23079-03 Interim Report 2 – contains ADA raw data
4. 5.3.3.5 ADA Addendum – contains PK/PD data

Clinical study 201 has ADA collection times at screening (or day 0 of first treatment), day 0 pre-treatment of each cycle, day 12 of each cycle, and at the end of treatment. Naxitamab PK/PD during the first cycle was assessed and graphed over time in Figure 1.

Figure 1. Naxitamab concentration in patients with and without ADA formation in Trial 201. Adapted from 5.3.3.5 ADA Addendum Figure 15.



The × indicates PK samples obtained at the day of or after ADA formation was positive.

Assessor comments: Naxitamab administration occurs at day 1, 3, and 5 of the cycle. The serum concentration of naxitamab maxes out at 100,000 ng/mL after the repeated drug administration at 1, 3, and 5 days. Because the serum concentration is consistent at 1, 3, and 5 days, the decay from day 5 until the start of the next cycle is expected to be consistent cycle to cycle. Subsequently, serum concentration is not expected to exceed 100,000 ng/mL at day 5 during cycle 1 through cycle 5, 2000 to 10,000 at day 12 (ADA collection timepoint), and 1000 ng/mL at day 1 of cycle 2-5 (ADA collection timepoint).

The drug tolerance of the validated ADA and NAb assays used to analyze clinical study 201 patient samples is 2000 ng/mL and 500 ng/mL, respectively.

1. For the ADA assay, the day 12 ADA sampling timepoint serum concentration (2000 to 10,000 ng/mL) is greater than the ADA drug tolerance (2000 ng/mL). Day 12 ADA sampling may result in interference and interpretation of ADA sampling at these timepoints should be considered if ADA patterns are abnormal, e.g. positive at day 1 of cycle 1 and cycle 2, but not day 12 of cycle 1.
2. For the NAb assay, the day 12 sampling timepoint serum concentration (2000 to 10,000 ng/mL) and the day 1 (cycle 2 through 5) sampling timepoint serum concentration (1000 ng/mL) are greater than the NAb assay drug tolerance (500 ng/mL). Subsequently, assay interference may occur at all current

sampling timepoints in the study. Of note, the NAb results in Table 1 below indicate that the NAb assay is able to identify NAb positive individuals; however, the serum concentration at the 'positive' timepoints are below the tolerance level for C2PREC timepoint (Cycle 2 day 1 pre-treatment collection) and 'negative' at D12C (Day 12 cycle 1) where serum concentration is above the tolerance limit. The serum concentration at the EOTC (end of treatment) timepoint is not specified.

To discuss this concern, we initiated a meeting with the assigned reviewers from clinical pharmacology, Dr. Catharine Bulik and Dr. Hong Zhao. They agreed that sampling was a concern and they will factor it into their overall assessment of the limited number of available samples. They informed us that they were considering post-marketing requirements for further immunogenicity studies.

In Trial 201, a total of 146 samples were drawn for ADA testing. Of the 146, 4 were screened indeterminate (1 of 2 duplicate wells positive) and 20 were screened positive. Of the 20 screening positive samples, 4 were confirmed positive. These samples were titered and submitted for testing in the NAb assay. The results of those 4 samples, from 2 patients, are provided in Table 1.

Table 1. Summary of ADA and NAb testing for patient's (b) (6).

Subject	Visit / barcode	ADA (Listing 16.2.8.1.1) (INTERIM ANTIBODY ANALYSIS REPORT NO.2, study# ACA23079-03)										NAB (INTERIM ANTIBODY ANALYSIS REPORT NO.2)		
		Screening			Confirmatory			Titer				rCP (RLU)	Response (RLU)	Result
		rCP (RLU)	Response (RLU)	Result	CP (fixed)	Inhibition (%)	Result	rCP	tCP	Titer	Titer w/ MRD=53 ^a			
(b) (6)	C2PREC/0128313-4460011	41.4	88.0	+	≥ 21.9%	47.8	+	40.4	44.7	16	848	9369.5	7467.5	+
	EOTC/0128433-4084011	41.4	141.5	+	≥ 21.9%	72.7	+	44.6	48.9	8	424	9369.5	8142.0	+
	D12C/0129252-4661011	70.1	71.5	+	≥ 21.9%	45.6	+	47.6	51.9	4	212	9473.3	11567.5	-
	C2PREC/0129252-4679011	70.1	83.0	+	≥ 21.9%	92.3	+	47.6	51.9	32	1696	9473.3	2946.0	+

C2PREC = cycle 2 day 1 pre-treatment collection; EOTC = end of treatment collection; D12C = cycle 1 day 12 collection

Assessor comments: *Using the validated ADA and NAb assays, patient samples from (b) (6) and (b) (6) are confirmed ADA+ and NAb+. Figure 1 shows that patient (b) (6) has decreased serum concentration of naxitamab compared to non-ADA+ samples, and the kinetics of patient (b) (6) are reduced further. These data correlate to the overall titer at cycle 2 day 1 for patient (b) (6) (titer of 848) and parent (b) (6) (titer of 1696). Importantly, the titer for patient (b) (6) at the end-of-treatment is lower than C2PREC, which indicates that ADA antibodies may diminish once treatment ends.*

Overall, the clinical data indicates that the ADA and NAb assays are able to identify ADA+ and NAb+ individuals and that the assay cut-points were set appropriately. It is noted that the clinical pharmacology review team is recommending a post-marketing requirement for further immunogenicity study and accumulation of more patient data. When the Sponsor proposes a plan for this PMR, they will take into account the assay drug tolerance and sampling points proposed by the Sponsor.

Executive Summary

The ADA and NAb assays described in method validation reports VCA 23074 and VCA 23075 respectively are suitable for testing the formation of ADA to naxitamab. Clinical data support assay suitability.

There are ongoing discussion between the application review team and Sponsor concerning the immunogenicity program given the number of patients available and future analysis. The Sponsor's proposal for continued study of the rates of immunogenicity will be analyzed with the assay validation data provided here in consideration.



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