CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761196Orig1s000

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:	April 19, 2021
Assessor:	Jim Barlow, RPh Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Massod Rahimi, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 4
Application:	BLA 761196
Applicant:	ADC Therapeutics SA
Submission Date:	September 21, 2020; December 3, 2020; January 4, 2021; March 12, 2021; April 12, 2021; April 16, 2021 and April 19, 2021
Product:	Zynlonta (Loncastuximab Tesirine-lpyl)
Dosage form(s):	For Injection
Strength and Container-Closure:	10 mg lyophilized powder in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application seeking the approval of loncastuximab tesirine-lpyl under the provision of Subpart E--Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL).
Recommendations:	The prescribing information, patient labeling, container labels and carton labeling 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 submitted April 19, 2021, the patient labeling submitted April 16, 2021 and the container labels and carton labeling submitted on March 12, 2021 were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Patient Information Leaflet (submitted on 1/4/2021)
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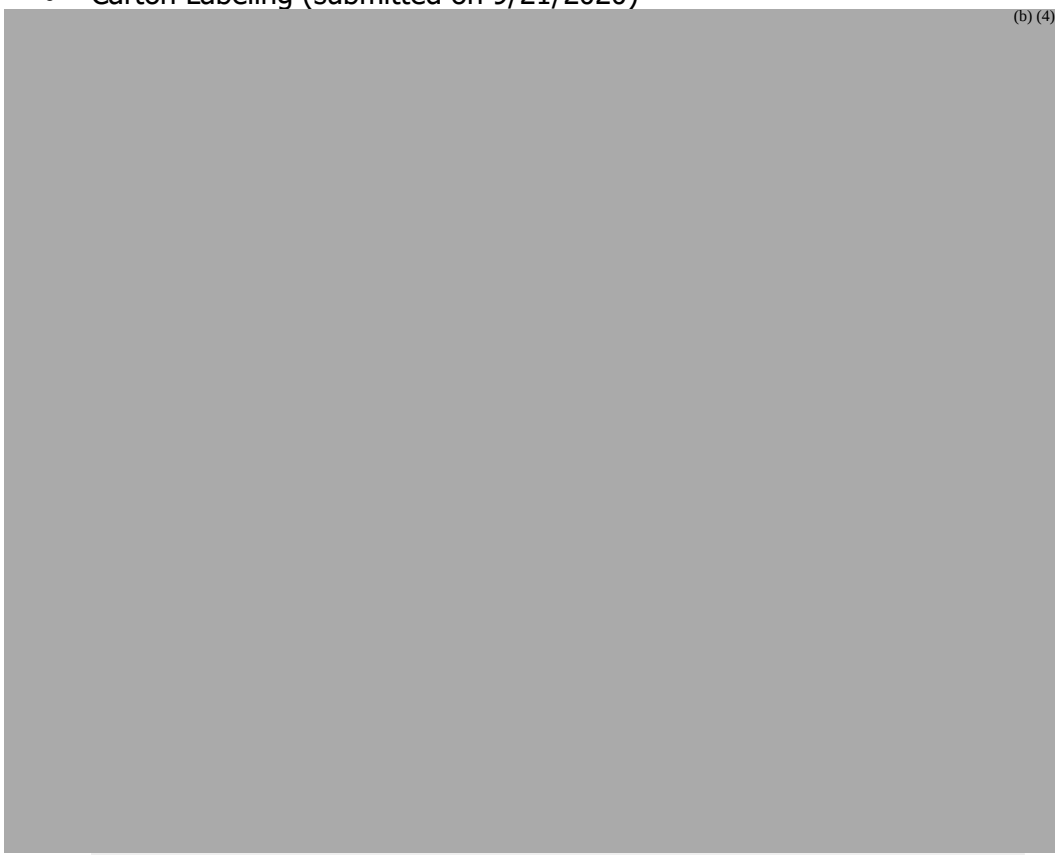
- Container Labels (submitted on 9/21/2020)

(b) (4)

- Carton Labeling (submitted on 9/21/2020)

(b) (4)



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

Container[4] Label Evaluation (Proprietary name granted 4/9/2021) (Suffix found conditionally acceptable in 3/5/2021)

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

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

Comment/Recommendation:
To Applicant: Per 21 CFR 610.60(c) If the container is capable of bearing only a partial label, the container shall show as a minimum … the name of the manufacturer.

Response: Applicant revised as requested by the Agency and included "Manufactured By" statement. Acceptable

Lot number or other lot identification (container label)	**Acceptable**

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

Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: DMEPA comment
The format for the expiration date is not defined. Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors. Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

Response: Applicant addressed as requested by the Agency. Acceptable

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

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

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

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: We recommend decreasing the prominence of the "Rx Only" statement by debolding as this information appears as prominent as other critical information on the principal display panel.

Response: Applicant revised as requested by the Agency. Acceptable

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

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

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

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

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

Response – Applicant confirmed. Acceptable

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes

	☐ No ☐ N/A

Comment/Recommendation: To Applicant: 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 Response: Applicant confirmed. Acceptable

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

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

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

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

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

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

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

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

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

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

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

Statement of Dosage (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

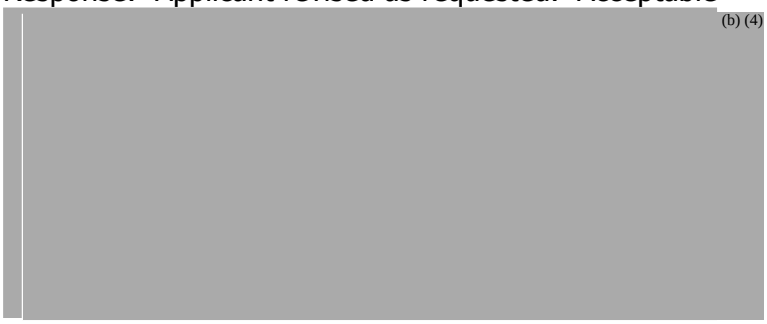
Comment/Recommendation: Not present on partial label.

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

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

Comment/Recommendation:
To applicant: The storage information is missing from the container label. Not including the storage information may lead to deteriorated drug medication errors. We recommend revising and including the storage statement, "Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake." On the side panel of the container label to be consistent with the Prescribing Information.

Response: Applicant revised as requested. Acceptable



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

Package[6] Labeling Evaluation

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

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

Comment/Recommendation: Acceptable

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

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

Comment/Recommendation: DMEPA comment
To Applicant: The format for the expiration date is not defined. Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors. Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

[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.

Response: Applicant addressed as requested by the Agency. Acceptable

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

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

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

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

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

Comment/Recommendation:
To Applicant: The statement, "Store refrigerated" is missing from the storage statement. Not including the "Store refrigerated" statement may result in the risk of the storage information being overlooked and lead to deteriorated drug medication errors. Revise and bold the storage statement to be consistent with language in the prescribing information as follows: "Store refrigerated at 2 °C to 8 °C (36 °F to 46 °F) in the original carton to protect from light prior to reconstitution. Do not freeze.

Response: The applicant revised as requested by the Agency. Acceptable

(b) (4)

[redacted]

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

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

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

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

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

Comment/Recommendation:
To applicant: Revise to include your inactive ingredients per 21 CFR 610.61, 21 CFR 201.100.

Response: Applicant revised to include inactive ingredients as requested by the Agency. Acceptable

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

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

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	☐ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: We recommend decreasing the prominence of the "Rx Only" statement by debolding as this information appears as prominent as other critical information on the principal display panel.

Response: Applicant revised as requested by the Agency. Acceptable

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

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

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

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

NDC numbers (package labeling)	**Acceptable**

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

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

Comment/Recommendation:
To Applicant: Revise to include the following:

Reconstitute each vial with 2.2 mL of Sterile Water for Injection, USP, resulting in a concentration of 5 mg/mL loncastuximab tesirine-lpyl with a pH of approximately 6.0. Swirl the vial gently. Do not shake. Do not expose to direct sunlight. Do not Freeze.

To Applicant: Revise to include the following "**Dilution: Must be further diluted with 5% Dextrose Injection, USP before use.**" to place emphasis on the correct solution that this drug product needs to be further diluted with on the carton.

Response: Applicant revised as requested by the Agency. Acceptable

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

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

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

Spanish-language (Drugs) (package labeling)	**Acceptable**

Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

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

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

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

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

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

Comment/Recommendation:
To Applicant: Consider revising the statement, "(b) (4): See prescribing information" to read "Dosage: See Prescribing Information." to be consistent with Physician Labeling Rule format.

Response: Applicant revised as requested. 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

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

Comment/Recommendation:
To Applicant: Revised to the correct dosing form and for the format to be in alignment with the Product Title Guidance.
"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:"
DOSAGE FORM TERMS FOR USE IN HUMAN DRUG PRODUCT LABELING.

Response: Revised as requested by the Agency. Acceptable

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

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

Comment/Recommendation:
To applicant: Revised to the correct dosing form and for the format to be in alignment with the Product Title Guidance
Response: Revised as requested. Acceptable

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

Comment/Recommendation:
To applicant: Revise to include important information for the healthcare provider and to be in alignment with more recently approved FDA labeling.

"No incompatibilities have been observed between (b) (4) and intravenous infusion bags with product-contacting materials of polyvinylchloride (PVC), polyolefin (PO), and PAB® (copolymer of ethylene and propylene)."

Response: The Applicant revised as requested by the Agency.

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**

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

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

Comment/Recommendation:
To Applicant: Per 21 CFR 201.57 (c)(12)(E), this section must include the pharmacological or therapeutic class of the drug. FDA preference is to use the pharmacological class used in the Highlights.

To Applicant: In the structural image, replace (b) (4) with "Loncastuximab" to utilize the name of the component.

Response: The applicant revised as requested. Acceptable

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

Comment/Recommendation:
To applicant: Revised to be in alignment with OSHA updated recommendations to read "Zynlonta is a hazardous drug." Firm revised as requested. ACCEPTABLE

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

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

Medication Guide Evaluation N/A

Patient Information Labeling Evaluation

PATIENT INFORMATION LABELING	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
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).	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Revised to the correct dosing form and for the format to be in alignment with the Product Title Guidance. "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:" DOSAGE FORM TERMS FOR USE IN HUMAN DRUG PRODUCT LABELING.

Response: Firm revised as requested by the Agency.

PATIENT INFORMATION LABELING	
STORAGE AND HANDLING	**Acceptable**
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)	☐ Yes ☐ No ☒ N/A

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

Comment/Recommendation: To applicant: Revised the inactive ingredients are listed in alphabetical order per USP General Chapters <1091> Labeling of Inactive Ingredients, and consistent with the Prescribing Information. Response: Revised as requested by the Agency. Acceptable

PATIENT INFORMATION LABELING	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Instructions for Use Evaluation N/A

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on April 19, 2021)
  \\CDSESUB1\evsprod\bla761196\0044\m1\us\draft-labeling-text-0044.doc
- Patient Information (submitted on April 16, 2021)
  \\CDSESUB1\evsprod\bla761196\0043\m1\us\draft-labeling-text-ppi-0043.doc
- Container Labels (submitted on March 12, 2021)

(b) (4)

- Carton Labeling (submitted on March 12, 2021)

(b) (4)

James Barlow

Digitally signed by James Barlow
Date: 4/19/2021 05:25:02PM
GUID: 508da70800028bcca2d0465dabab258f

Massod Rahimi

Digitally signed by Massod Rahimi
Date: 4/19/2021 05:26:01PM
GUID: 542e18bc0004452462912a2ae67666a9

Orphan Drug
Priority Review
Recommendation: Approval

BLA Number: 761196
Review Number: First round
Review Date: April 8, 2021

Drug Name/Dosage Form	ZYNLONTA™ (loncastuximab tesirine-lpyl)/for injection, lyophilized powder in a single-dose vial
Strength/Potency	10 mg (5 mg/mL after reconstitution with 2.2 mL sterile WFI)
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	For treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma
Applicant/Sponsor	ADC Therapeutics SA

Product Overview:

Loncastuximab tesirine-lpyl (ADCT-402) is an antibody-drug conjugate (ADC) comprised of a recombinant humanized IgG1κ monoclonal antibody (mAb) against human CD19 conjugated through interchain cysteines to pyrrolobenzodiazepine (PBD) dimer molecules via a protease-cleavable Val-Ala dipeptide-containing linker by thiol-maleimide chemistry. CD19 is a cell surface glycoprotein present on early pre-B and mature B lymphocytes and on several B-cell malignancies, including leukemia and NHL cells. Upon binding of loncastuximab tesirine to CD19, the molecule is internalized and the linker is cleaved by lysosomal proteases to enable release of the PBD dimer. The PBD dimer binds to the DNA minor groove and forms (highly toxic) DNA interstrand crosslinks, subsequently inducing cell cycle arrest and cell death. The loncastuximab tesirine-lpyl manufacturing process (b) (4) (b) (4).

Loncastuximab tesirine-lpyl drug product, Zynlonta, is supplied as a sterile, preservative-free, white to off-white lyophilized cake or powder in a single-dose vial for intravenous use after reconstitution and further dilution. Each vial contains 10 mg loncastuximab tesirine-lpyl, L-histidine (2.8 mg), L-histidine monohydrochloride (4.6 mg), sucrose (119.8 mg), and polysorbate 20 (0.4 mg). After reconstitution with 2.2 mL of Sterile Water for Injection, USP, the resulting concentration is 5 mg/mL with a pH of 6.0.

Quality Review Team:

Discipline/subject	Reviewer	Branch/Division
mAb Intermediate Drug Substance Drug Product	Massod Rahimi	OPQ/OBP/DBRR IV
Drug-linker intermediate Drug Substance	Rohit Tiwari	OPQ/ONDP/DNDAPI/NDB1
Drug Substance (microbiology, facility) Drug Product (microbiology, facility)	Bo Chi Amy Devlin	OPQ/OPMA/DBM OPQ/OPMA/DBM
Immunogenicity	Massod Rahimi	OPQ/OBP/DBRR IV

Labeling	James Barlow	OPQ/OBP
Team Leads: OBP Product quality ONDP OPMA	 Bazarragchaa Damdinsuren Ali Al Hakim Candace Gomez-Broughton (micro) Zhong Li (facility)	 OPQ/OBP/DBRR IV OPQ/OPMA/DBM OPQ/OPMA/DBM
CMC RPBM	Anita Brown	OPQ/OPRO
Application Team Lead	Bazarragchaa Damdinsuren	OPQ/OBP/DBRR IV

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Jennifer Lee	OND/ORO/DROOD
Cross-disciplinary Team Lead	Nicholas Richardson	OND/OOD/DHM1
Medical Officer	Candis Morrison	OND/OOD/DHM1
Pharmacology/Toxicology	Natalie Simpson	OND/OOD/DHM1
Clinical Pharmacology	Krithika Shetty	OND/OCP
Statistics	Jay Zhao	OND/OB

1. Names:
   a. Proprietary Name: Zynlonta
   b. Trade Name: Zynlonta
   c. Non-Proprietary Name / USAN/INN Name: loncastuximab tesirine-lpyl / loncastuximab tesirine
   d. CAS Name: 1879918-31-6
   f. Chemical Name: ADCT-402, a humanized IgG1k, linked to SG3249 drug-linker intermediate
   h. OBP systematic name: CONJ: MAB HUMANIZED (IGG1) ANTI P15391 (CD19_HUMAN); pyrrolobenzodiazepine [ADCT402]

Submissions Reviewed:

Submission SN (subject)	Submission Date
STN 761196 / SN0001 (Original submission)	August 7, 2020
STN 761196 / SN0003 (Response to IR #1 and #2)	October 8, 2020
STN 761196 / SN0010 (Response to IR #3)	November 25, 2020
STN 761196 / SN0012 (Response to IR #4)	December 9, 2020
STN 761196 / SN0013 (Response to IR #4)	December 16, 2020
STN 761196 / SN0014 (Response to IR #5 and #6)	December 18, 2020
STN 761196 / SN0020 (Response to IR #7)	January 21, 2021
STN 761196 / SN0021 (Response to IR #5 and #7)	January 28, 2021
STN 761196 / SN0024 (Response to IR #9)	February 16, 2021
STN 761196 / SN0025 (Response to IR #8)	February 19, 2021
STN 761196 / SN0027 (Response to IR #10)	February 22, 2021
STN 761196 / SN0029 (Response to IR #11)	March 3, 2021
STN 761196 / SN0031 (Response to IR #12)	March 9, 2021
STN 761196 / SN0032 (Response to IR #13)	March 11, 2021
STN 761196 / SN0034 (Response to IR #14, 15)	March 24, 2021
STN 761196 / SN0036 (Response to IR #12, 9)	April 5, 2021

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 Reviewed	Comments (status):
(b) (4)	V	(b) (4)		3	N/A	N/A	No assessment required as the relevant information was in the BLA
	III			3	N/A	N/A	No assessment required at this time as the relevant information related to compatibility with the product was in the BLA
	III			3	N/A	N/A	No assessment required as this DMF is CBER-specific; instead DMF (b) (4) is evaluated (update and LOA provided in sequence 0024)
	III			3	N/A	N/A	No assessment required at this time as the relevant information related to compatibility with the product was in the BLA
	III			3	N/A	N/A	No assessment required at this time as the relevant information related to compatibility with the product was in the BLA
	III			3	N/A	N/A	No assessment required at this time as the relevant information related to compatibility with the product was in the BLA

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

B. Other documents: IND 126138

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion: The applicant claims a categorical exclusion per 21 CFR 25.31(c) from the environmental assessment requirements of 21 CFR 25.20. Approval of this BLA will increase the use of substances that occur naturally in the environment, but the action does not alter significantly the concentration or distribution of the substances, their metabolites, or degradation products in the environment. Categorical Exclusion is appropriate for this product.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761196 for Zynlonta (loncastuximab tesirine-lpyl) manufactured by ADC Therapeutics SA. The data submitted in this application are adequate to support the conclusion that the manufacture of Zynlonta is well-controlled and leads to a product that is pure and potent. OPQ recommends that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing location:
  - Monoclonal Antibody Intermediate: (b) (4)
  - Drug Linker Intermediate: (b) (4) (b) (4)
  - Drug Substance: (b) (4)
  - Drug Product: (b) (4) (b) (4).
- Fill size and dosage form: 10 mg, for injection, lyophilized powder in a single-dose vial
- Dating period:
  - Monoclonal Antibody Intermediate: (b) (4)
  - Drug Linker Intermediate: (b) (4)
  - Drug Substance: (b) (4) months when stored at (b) (4)
  - Drug Product: 24 months when stored at 5 ± 3°C
  - For packaged products: Not packaged
  - Stability Option:
    - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your antibody intermediate, drug linker intermediate, drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release: Yes
  - Rationale: specified product
    Note: Zynlonta is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

Zynlonta (loncastuximab tesirine-lpyl) is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma. Loncastuximab tesirine-lpyl received Orphan drug designation on June 8, 2017 under IND 126138. The pivotal clinical study (a Phase 2, single-arm, open-label, multi-center study ADCT-402-201) supporting the BLA showed overall response rate of 48% and estimated duration of response for 10.25 months with Zynlonta (150 µg/kg Q3W for 2 cycles, then 75 µg/kg Q3W regimen) in relapsed or refractory DLBCL patients. The most common adverse reactions (and laboratory abnormalities), including were thrombocytopenia, increased gamma glutamyl transferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain, are described in the labeling.

The OPQ assessment of manufacturing has identified that the methodologies and processes used for mAb intermediate, drug-linker intermediate, drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The mAb intermediate manufacturing process is robust for inactivation and removal of adventitious agents. The BLA is recommended for approval from a microbiology product quality and sterility assurance perspective. All facilities used for the manufacture and quality control testing were found acceptable for the proposed operations (refer to sections H and I of this document).

The immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) in presence of loncastuximab tesirine-lpyl at plasma concentrations. ADAs were not characterized or assessed for neutralizing activity as the characterization and neutralizing antibody (NAb) assays were not submitted to the BLA. The BLA assessment team concluded that a validated NAb was not necessary for approval of the BLA as no patients were found to have treatment-emergent ADAs in the pivotal clinical study. As a validated NAb assay may be required for future clinical NAb assessment, validation of the NAb assay is agreed with the Applicant as PMC#2.

The technical assessments for product quality and immunogenicity assays (by OBP), small molecule product quality (by ONDP), microbiological drug substance and drug product, facility (by OPMA), and OBP labeling are located as separate documents in Panorama.

D. Recommendation on Post-Marketing Commitments:

1. Complete the qualification of endotoxin test method for the in-process [(b) (4)] samples using samples from two additional loncastuximab antibody lots. In addition, complete the qualification of bioburden test method for the in-process samples using samples from two additional loncastuximab antibody lots. The final report should include method qualification reports for endotoxin and bioburden tests.
2. Develop and validate an assay to evaluate the neutralizing capacity of anti-drug antibodies (ADAs) detected in the patient samples. The assay should be capable of sensitively detecting neutralizing ADAs in the presence of loncastuximab tesirine levels that are expected to be present in serum at the time of patient sampling. Appropriately bank samples from ongoing clinical trials to evaluate neutralizing antibodies (nAb) in all confirmed ADA-positive samples using the validated assay and correlate with safety and efficacy of loncastuximab tesirine. The final report should include nAb assay validation report and assay standard operating procedure.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 is a summary of product-related critical quality attributes (CQA), intrinsic to loncastuximab tesirine-lpyl. The table includes the identification of the various attributes along with their risk management.

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

CQA type	CQA	Risk	Origin	Control Strategy
Identity	Identity	Safety, potency/ DP failure	Intrinsic to the molecule	[(b) (4)]

				(b) (4)
Structure	Primary structure	Potency, immunogenicity, safety	Cell line, production and purification processes	
	Higher order structure	Potency, immunogenicity, safety	Cell line, production and purification processes	
	(b) (4)	PK	mAb and DS manufacturing processes (production and purification)	
Size Heterogeneity (product-related impurity)	HMW species/ aggregates	Potency, PK, immunogenicity, safety	mAb, DS, DP manufacturing processes (production, purification (low pH, holds) and conjugation), and on stability	
	LMW species	Potency, immunogenicity	mAb, DS, DP manufacturing processes (holds), and on stability	
Charge Heterogeneity	Acidic species	PK, safety	Cell culture at production bioreactor, purification, and conjugation (DS) processes, and on stability	
Biological activity/Potency	Antigen binding	Biological activity /DP failure	Intrinsic to the molecule. (May be affected by mAb and DS manufacturing processes)	
	Cytotoxicity	Biological activity, efficacy and safety /DP failure	Intrinsic to the molecule. Production, purification and conjugation processes, and on stability	
	FcRn binding	PK	Intrinsic to the molecule. Production process	
Glycosylation	(b) (4)	PK	Intrinsic to the molecule. Production processes (production bioreactor and cell line)	
Conjugate Variants	DAR and DLD	Potency, potentially in efficacy and safety	DS manufacturing (conjugation) process, may change on stability	

(b) (4), DS - drug substance, DP - drug product, DAR - drug-antibody ratio, DLD - drug load distribution

B. (b) (4)

(b) (4)

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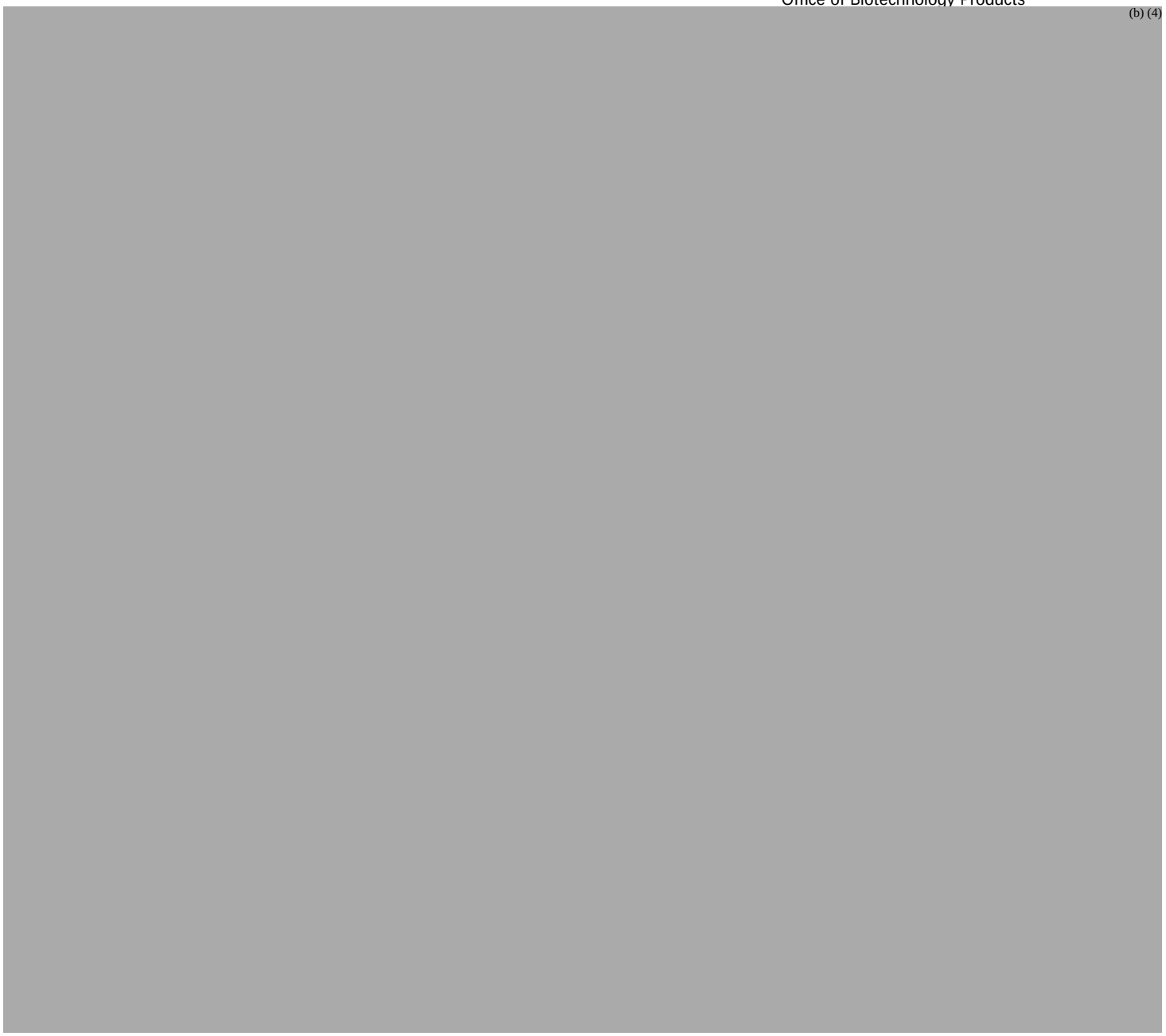
(b) (4)



D. Drug Substance (Loncastuximab tesirine-lpyl) Quality Summary

Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for the ADC drug substance-specific CQAs.

Table 4: Drug Substance CQA# Process Risk Identification and Lifecycle Knowledge Management.

CQA type	CQA	Risk	Origin	Control Strategy
DS Composition	Appearance (color, clarity)	Potency, safety	Product and formulation, may change on stability	(b) (4)

				(b) (4)
	Protein concentration	Efficacy (inaccurate dosing impacting PK), safety	DS manufacturing process (final formulation)	
	Osmolality	Product stability	DS formulation	
	pH	Potency, product stability	Formulation (UF/DF, buffer preparation), may change on stability	
	Polysorbate 20	Particle formation, product stability	Raw material control, manufacturing process (formulation)	
Process-related impurities	Unconjugated drug-linker/Free drug	Safety	DS manufacturing process (conjugation and purification)	
	Unconjugated mAb	Potency, safety	DS manufacturing process (conjugation and purification)	
	(b) (4)	Safety	DS manufacturing process (conjugation and purification)	
	(b) (4)	Safety	DS manufacturing process (conjugation and purification)	
	Leachables	Immunogenicity, safety	Throughout manufacturing process, CCS	
Impurity/ Conjugate variants	Free drug-linker degradants	Safety	DS manufacturing process (conjugation and purification by RP-HPLC), may form on stability	
	Drug degradation (aromatization)	Potency	DS manufacturing process (conjugation and purification by RP-HPLC), may change on stability	
	Linker hydrolysis and drug degradation (+2 Da, fragmentation, oxidation)	Potency, Safety	DS manufacturing process (conjugation and purification by RP-HPLC), may change on stability	
Bacterial Endotoxins (contaminant)	Endotoxin	Safety, purity	Raw materials and manufacturing process	

Bioburden (contaminant)	Bioburden	Safety, purity, efficacy (degradation or modification of the product)	Raw materials and manufacturing process	(b) (4)

[#] Includes the active pharmaceutical ingredient CQAs presented in Table 1.

- Description: Loncastuximab tesirine-lpyl (ADCT-402) is an ADC comprised of a humanized IgG1κ mAb (RB4v1.2) against human CD19 conjugated through interchain cysteines to drug linker (SG3249) consisting of PBD dimer molecules and a protease-cleavable Val-Ala dipeptide-containing linker. Loncastuximab tesirine-lpyl has a molecular weight of ~150.8 kDa with predominantly N-linked glycosylation G0F on each mAb heavy chain and an average DAR of 2.3, and its extinction coefficient is 1.9 mL/mg/cm.
- Mechanism of Action (MoA): Upon binding to cell-surface CD19, loncastuximab tesirine is internalized and the linker is cleaved by lysosomal proteases to enable release of the PBD dimer. The PBD dimer binds to the DNA minor groove and forms toxic DNA interstrand crosslinks, subsequently inducing cell cycle arrest and cell death. ADCC and CDC are not a part of the MoA of loncastuximab tesirine.
- Potency Assay: There are two potency assays used in DS and DP release and stability testing.
  - A cell-based cytotoxicity bioassay that measures the relative cytotoxicity of loncastuximab tesirine to CD19-expressing Ramos-1 (human Burkitt's B-cell lymphoma) cells.
  - A cell-based antigen binding assay that measures the relative (competitive) binding to CD19 on Ramos-1 cells (used for (b) (4) testing).
- Reference Materials: (b) (4) (b) (4)
- Critical starting materials or intermediates: (b) (4) (b) (4)
- Manufacturing process summary: The loncastuximab tesirine drug substance manufacturing process consists of (b) (4) (b) (4)

(b) (4)

The loncastuximab tesirine-lpyl drug substance manufacturing process development is based on process characterization and process validation studies. The overall control strategy is adequate.

- Container closures: Loncastuximab tesirine-lpyl drug substance is stored in (b) (4) (b) (4) bottles with HDPE closure.
- Dating period and storage conditions: A shelf-life of (b) (4) months when stored at ≤ (b) (4) is acceptable based on available stability data from the drug substance batches manufactured by the commercial process.

E. Drug Product (Zynlonta) Quality Summary:

Table 5 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 5: Drug Product CQA# Identification, Risk, and Lifecycle Management

CQA type	CQA	Risk	Origin	Control Strategy
DP Composition and Strength	Appearance and color of lyophilized powder	May not have direct link	Manufacturing process (lyophilization), formulation, may change on stability	(b) (4)
	Appearance after reconstitution (color, clarity)	Potency, safety	Manufacturing process, product on stability and formulation	
	Reconstitution time	May not have direct link	Manufacturing process (lyophilization), formulation, may change on stability	
	Protein Concentration	Efficacy (inaccurate dosing impacting PK), and safety	DS material, DP manufacturing process (fill)	
	Osmolality	Safety (patient discomfort), product stability	DP formulation	

	pH	Potency, product stability	DP manufacturing process (DS material, DP fill)	(b) (4)
	Polysorbate 20	Particle formation, product stability	Raw material control, Manufacturing process (DS formulation, DP fill)	
	Water content	May affect product stability	Manufacturing process (lyophilization), formulation, may change on stability	
	Extractable volume (content in vial)	Dosing (efficacy)	Extractable volume: assured by preparation instruction in USPI. Content: DS material, DP manufacturing process (fill)	
Particles	Visible and Subvisible Particles	Safety, immunogenicity	Manufacturing process, CCS and product on stability	
(b) (4) impurities	Leachables	Immunogenicity, safety	Throughout manufacturing process, CCS	
	Unconjugated drug-linker/Free drug	Safety	DS material, may change on stability	
	Unconjugated mAb	Potency, safety	DS material, may change on stability	
Impurity/ Conjugate variants	Free drug-linker degradants	Safety	DS material, may form on stability	
	Drug degradation (aromatization)	Potency	DS material, may change on stability	
	Linker hydrolysis and drug degradation (+2 Da, fragmentation, oxidation)	Potency, Safety	DS material, may change on stability	
Sterility (contaminant)	Sterility	Safety (infection), efficacy (degradation or modification of the product)	Contamination may be introduced throughout the DP manufacturing process, container closure failure	
	Container Closure Integrity	Safety (loss of sterility), efficacy (change on product strength due to evaporation or leakage)	Container closure breaches during storage	
Endotoxin (contaminant)	Endotoxin	Safety, purity	Raw materials and manufacturing process	
Bioburden (contaminant)	Bioburden	Safety, purity, efficacy (degradation or	Raw materials and manufacturing process	

		modification of the product)		

[#] Includes the active pharmaceutical ingredient CQAs presented in Table 1.

- Potency and Strength: 10 mg (5 mg/mL after reconstitution with 2.2 mL sterile WFI)
- Summary of Product Design: A sterile, preservative-free, white to off-white lyophilized powder in a single-dose vial for intravenous use after reconstitution and further dilution.
- List of Excipients: L-histidine, L-histidine monohydrochloride, sucrose, polysorbate 20.
- Reference Materials: Same as the loncastuximab tesirine-lpyl drug substance RSs.

  Manufacturing process summary: The Zynlonta drug product manufacturing includes (b) (4) (b) (4)

  Additional manufacturing process details can be found in the drug product quality assessments by Dr. Massod Rahimi.

  (b) (4) (b) (4) Bioburden and endotoxin are tested during manufacture, and sterility and endotoxin are tested at release.

  Container closure integrity is tested using a validated (b) (4) analysis method as part of the stability program. Additional details can be found in the drug product microbiology assessment and addendum by Dr. Amy Devlin.

  Zynlonta drug product manufacturing process development is based on process characterization and process validation studies. The overall control strategy is adequate.

- Container closure: The DP container/closure system consists of a (b) (4) (b) (4) glass vial (b) (4) stopper (b) (4) (b) (4) (b) (4), and (b) (4) seal (b) (4) (b) (4).
- Dating period and storage conditions: A shelf-life of 24 months when stored at 5 ± 3°C is acceptable based on available stability data from the drug product batches manufactured by Process B and commercial processes.

F. Novel Approaches/Precedents: None

G. Any Special Product Quality Labeling Recommendations: (see details in CDR. James Barlow's labeling assessment)

In Prescribing Information:

- Zynlonta is a hazardous drug. Follow applicable special handling and disposal procedures.
- Do not shake. Do not expose to direct sunlight.
- Use reconstituted Zynlonta immediately. If not used immediately, store the reconstituted solution in the vial for up to 4 hours refrigerated at 2°C to 8°C (36°F to 46°F) or room temperature 20°C to 25°C (68°F to 77°F). Do not freeze.

- Add the calculated dose volume of Zynlonta solution into a 50 mL infusion bag of 5% Dextrose Injection, USP.
- If not used immediately, store the diluted Zynlonta infusion solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature 20°C to 25°C (68°F to 77°F) for up to 8 hours. Discard if storage time exceeds these limits. Do not freeze.

In Carton and container label:

- Reconstitution: Reconstitute with 2.2 mL Sterile Water for Injection, USP.
  Dilution: Must be further diluted with 5% Dextrose Injection, USP.
- Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

H. Establishment Information:

Overall Recommendation: Approve

RB4v1.2 mAb Intermediate

Function	Site Information	FEI Number	Preliminary Assessment / Final Recommendation
		(b) (4)	Approve - Based on Inspection
			Approve - Based on Profile
			Approve - Based on Profile
			Approve - Based on Profile
			No Evaluation Necessary

SG3249 Drug Linker Intermediate

Function	Site Information	FEI Number	Preliminary Assessment / Final Recommendation
		(b) (4)	Approve - Based on Profile and District File Review
			Approve - Based on Profile and District File Review
			No Evaluation Necessary

Loncastuximab Tesirine-lpyl Drug Substance

Function	Site Information	FEI	Preliminary Assessment / Final Recommendation
		(b) (4)	Approve – Based on 704 (a) (4) manufacturing record review
			Approve - Based on Profile

Zynlonta Drug Product			
Function	Site Information	FEI Number	Preliminary Assessment / Final Recommendation
[redacted] (b) (4)			Approve - based on previous history and waiver granted by OPMA and OBP
			Approve - Based on Profile and District File Review
			Approve - Based on Profile

DS - drug substance, DP - drug product, IPC – in-process control, MCB - Master Cell Bank, WCB - Working Cell Bank

I. Facilities:

A pre-license inspection (PLI) of [redacted] (b) (4) was conducted by CDER (by Michael Shanks, OPQ/OPMA/DBM and Massod Rahimi, OPQ/OBP/DBRRIV) on February 4-11, 2021 in support of BLA 761196 for loncastuximab mAb intermediate. The inspection was system-based and covered quality, facilities and equipment, production, materials, and laboratory control systems. No FDA Form 483 was issued, and the inspection was classified as NAI. Three verbal discussion items were communicated to the firm.

A PLI for the drug substance manufacturing facility [redacted] (b) (4) was performed using the Agency's authority under Section 704(a)(4) of the FD&C Act by assessment of manufacturing records from the manufacturing facility in lieu of performing an on-site inspection. On December 5, 2020 and January 25, 2021, the Agency requested pre-inspection audit documents in support of loncastuximab tesirine drug substance manufacturing, testing, and storage at [redacted] (b) (4). The firm submitted the requested documents on January 18, 25 and 28, 2021. The assessment of manufacturing site records conducted by Bo Chi (OPQ/OPMA/DBM) and Massod Rahimi (OPQ/OBP/DBRRIV) concluded that the drug substance manufacturing facility is acceptable to support the approval of BLA 761196.

The PLI of the drug product manufacturing site, [redacted] (b) (4), was waived as the fill line is used for the commercial manufacture of license products and the facility has an acceptable compliance history.

The compliance recommendations for the other facilities described in the tables (section H), which are not inspected within scope of this BLA, are for approval.

J. Lifecycle Knowledge Management:

a. mAb Intermediate:

[redacted] (b) (4)

(b) (4)

b. Drug Linker Intermediate:

(b) (4)

c. Drug Substance:
    i. Protocols approved (section in eCTD):
        1. Stability of reference standards (3.2.S.5 - DS)
        2. Qualification and stability of future reference standards (3.2.S.5 - DS)
        3. Ongoing primary stability study (3.2.S.7.2 - DS)
        4. Post-approval annual stability (3.2.S.7.2 - DS)
    ii. Outstanding review issues/residual risk: None
    iii. Future inspection points to consider: None

d. Drug Product:
    i. Protocols approved (section):
        1. Ongoing primary stability study (3.2.P.8.2)
        2. Post-approval annual stability (3.2.P.8.2)
    ii. Outstanding review issues/residual risk: None
    iii. Future inspection points to consider: None

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

/s/

BAZARRAGCHAA DAMDINSUREN
04/08/2021 06:10:51 PM

ALI H AL HAKIM
04/09/2021 09:28:30 AM

ZHONG LI
04/09/2021 03:13:18 PM

CANDACE GOMEZ-BROUGHTON
04/09/2021 03:17:56 PM

PRODUCT QUALITY MICROBIOLOGY/FACILITY ASSESSMENT
Memorandum of Review to the File (Addendum)

Application ID	BLA 761196
Submission Type	Original BLA
Drug Product Name	Loncastuximab tesirine-lpyl (Zynlonta™)
Strengths	10 mg/vial
Dosage Form	Lyophilized powder
Administration Route	Intravenous
Indication	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after at least two prior systemic therapies
Applicant Name	ADC Therapeutics SA
US License Number	2166
Application Type	351 (a)
Primary Reviewer	Amy Devlin, Microbiologist, Ph.D.
Secondary Reviewer	Candace Gomez-Broughton, Branch Chief, Ph.D.
Goal Date	May 21, 2021

Recommendation for Approvability:

- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.
- Manufacturing Facility Assessment Recommendation: Approve.
- The drug product part of this BLA was reviewed from a sterility assurance and product quality microbiology perspective and is recommended for Approval.

This addendum assesses the responses to the following comments sent on 02/05/2021 and on 02/22/2021 regarding rabbit pyrogen test and shipping qualification:

02/05/2021: *Provide shipping qualification data. Clarify whether container closure integrity testing (CCIT) was performed as part of shipping validation and describe the test method (e.g., test parameters, time, and pressure/vacuum cycles, positive/negative controls, etc.) and test results. Describe the shipping container used to transport DP vials and the minimum and maximum loads. Provide the acceptance criterion for shipping duration. Provide information and data of the development study to demonstrate that the DP temperature is maintained at 2-8°C when exposed to the worst-case summer and winter conditions the DP vials may encounter during transportation. Provide the report for the transport verification study.*

02/22/2021: *Provide a description and summary results from the Rabbit Pyrogen test performed on three lots of drug product to demonstrate non-pyrogenicity per 21 CFR 610.13(b). Once this is demonstrated, bacterial endotoxin test can then be used as a release test for the drug product. In your response, provide a timeline for when the studies will be completed, and results submitted to the BLA.*

Amy Devlin

Digitally signed by Amy Devlin
Date: 4/08/2021 03:44:58PM
GUID: 5bad1e590013e11cfb94f1c3a1ef8f84

Candace Gomez-Broughton

Digitally signed by Candace Gomez-Broughton
Date: 4/08/2021 04:18:07PM
GUID: 508da7470002bfa96430b4eae8e26771

BLA STN 761196

ZYNLONTA™ (loncastuximab tesirine-lpyl)

Manufacturer: ADC Therapeutics SA

Massod Rahimi, Ph.D., Primary Assessor
Bazarragchaa Damdinsuren, M.D., Ph.D., Application Technical Lead

Division of Biotechnology Review and Research IV (DBRR IV)
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

OBP CMC Assessment Data Sheet

1. BLA: STN 761196

2. ASSESSMENT DATE: March 13, 2021

3. PRIMARY ASSESSMENT TEAM:

Product Quality Team:

OPQ/OBP:	Massod Rahimi (mAb intermediate, DS, DP, immunogenicity), James Barlow (labeling), Bazarragchaa Damdinsuren (ATL)
OPQ/ONDP:	Rohit Tiwari (drug-linker intermediate, DS, DP), Ali Al Hakim (BC)
OPQ/OPMA:	Bo Chi (DS microbiology and facility), Amy Devlin (DP microbiology and facility), Candace Gomez-Broughton (microbiology TL), Zhong Li (facility TL)
OPQ/OPRO:	Anita Brown (RBPM)
Clinical:	Candis Morrison, Nicholas Richardson (TL), Jennifer Lee (RPM)
Pharmacology/Toxicology:	Natalie Simpson, Brenda Gehrke (TL)
Statistics:	Jay Zhao, Yu-Te Wu (TL)
Clinical Pharmacology:	Krithika Shetty, Ruby Leong (TL)
OOD Safety:	Shanti Marur, Felicia Diggs (SRPM), Liz Everhart (OOD ADL)

4. MAJOR GRMP DEADLINES:

Filing Meeting:	November 9, 2020
Mid-Cycle Meeting:	January 6, 2021
Late-Cycle Meeting:	March 5, 2021
Wrap-Up Meeting:	March 23, 2021
Primary Assessment Due:	March 12, 2021
CDTL Memo Due:	April 12, 2021
PDUFA Goal Date:	May 21, 2021 (Planned Action Date: April 21, 2021)

5. COMMUNICATIONS WITH SPONSOR AND OND:

Communication/Document:	Date:
Information Request #1	October 1, 2020
Information Request #2	October 2, 2020
Information Request #3	November 11, 2020
Information Request #4	November 25, 2020
Information Request #5	December 4, 2020
Information Request #6	December 15, 2020
Information Request #7	January 11, 2021
Information Request #8	February 4, 2021
Information Request #9	February 5, 2021
Information Request #10	February 12, 2021
Information Request #11	February 22, 2021
Information Request #12	February 26, 2021
Information Request #13	March 8, 2021

6. SUBMISSION(S) ASSESSED:

Submission:	Date Received:	Assessment Completed (yes or no):
STN 761196 / SN0001	August 7, 2020	Yes
STN 761196 / SN0003 (Response to IR #1 and IR #2)	October 8, 2020	Yes
STN 761196 / SN0010 (Response to IR #3)	November 25, 2020	Yes
STN 761196 / SN0012 (Response to IR #4)	December 9, 2020	Yes
STN 761196 / SN0013 (Response to IR #4)	December 16, 2020	Yes
STN 761196 / SN0014 (Response to IR #5 and IR #6)	December 18, 2020	Yes
STN 761196 / SN0020 (Response to IR #7)	January 21, 2021	Yes
STN 761196 / SN0021 (Response to IR #5 and IR #7)	January 28, 2021	Yes
STN 761196 / SN0024 (Response to IR #9)	February 16, 2021	Yes
STN 761196 / SN0025 (Response to IR #8)	February 19, 2021	Yes
STN 761196 / SN0027 (Response to IR #10)	February 22, 2021	Yes
STN 761196 / SN0029 (Response to IR #11)	March 3, 2021	Yes
STN 761196 / SN0031 (Response to IR #12)	March 9, 2021	Yes
STN 761196 / SN0032 (Response to IR #13)	March 11, 2021	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

a. Proprietary Name: ZYNLONTA
b. Trade Name: ZYNLONTA™
c. Non-Proprietary/USAN: loncastuximab tesirine-lpyl/loncastuximab tesirine
d. CAS Registry Number: 1879918-31-6
e. Common Name: ADCT-402
f. INN Name: loncastuximab tesirine
g. OBP Systematic Name: CONJ: MAB HUMANIZED (IGG1) ANTI P15391 (CD19_HUMAN); pyrrolobenzodiazepine [ADCT402]

8. PHARMACOLOGICAL CATEGORY: CD19-directed antibody and alkylating agent conjugate (ADC)

9. DOSAGE FORM: For injection, lyophilized powder in a single-dose vial for reconstitution and further dilution

10. STRENGTH/POTENCY:

(i) The strength/concentration of the Drug Product: 10,000 μg (5,000 μg/mL after reconstitution with 2.2 mL SWFI)
(ii) Type of potency assays: Cell-based CD19 binding immunoassay, cell-based cytotoxicity assay

11. ROUTE OF ADMINISTRATION: Intravenous infusion

12. REFERENCED DRUG MASTER FILES:

DMF#	DMF Holder:	Item Referenced:	Letter of Cross-Reference:	Comments (status):
(b) (4)			Yes	Deferred to OPMA
			Yes	No assessment required at this time as the relevant information related to compatibility with the product was in the BLA
			Yes	Deferred to OPMA
			Yes	No assessment required at this time as the relevant information related to compatibility with the product was in the BLA
			Yes	No assessment required at this time as the relevant information related to compatibility with the product was in the BLA
			Yes	Deferred to OPMA

13. INSPECTIONAL ACTIVITIES:

An on-site pre-license inspection (PLI) was conducted by Michael Shanks (CDER, OPQ, OPMA) and Massod Rahimi (CDER, OPQ, OBP) from February 4, 2021 to February 11, 2021 for the mAb intermediate manufacturing facility (b) (4). The inspection covered quality, facilities/equipment, production, materials, and laboratory control systems. A Form FDA 483 was not issued to the firm at the end of the inspection. Three verbal discussion items were discussed

with the firm at the close-out of the inspection. Initial facility recommendation is "No Action Indicated (NAI)". The proposed mAb intermediate manufacturing facility is found to be acceptable to support the approval of BLA 761196.

In lieu of an on-site PLI for the drug substance manufacturing facility - (b) (4) (b) (4) an assessment of manufacturing site records according to Section 704(a)(4) was conducted by Bo Chi (CDER, OPQ, OPMA) and Massod Rahimi (CDER, OPQ, OBP) in January of 2021. The assessment of manufacturing site records found the documents adequate. The proposed drug substance manufacturing facility is found to be acceptable to support the approval of BLA 761196.

The PLI of the drug product manufacturing site, (b) (4) was waived by OPMA and OBP as the fill line is used for the commercial manufacture of license products and the facility has an acceptable compliance history. The proposed drug product manufacturing facility is found to be acceptable to support the approval of BLA 761196.

14. CONSULTS REQUESTED BY OBP: None

15. QUALITY BY DESIGN ELEMENTS: None

16. PRECEDENTS: None

17. ADMINISTRATIVE:

Signature Block

Name and Title	Signature and Date
Bazarragchaa Damdinsuren, M.D., Ph.D. Application Technical Lead, DBRR IV/OBP/OPQ	See attached
Massod Rahimi, Ph.D. Primary Assessor, DBRR IV/OBP/OPQ	See attached

CC Block

Recipient
Jennifer Lee, Clinical Division BLA RPM
OBP/DBRR IV File/BLA STN 761196

Summary of Quality Assessments

I. Primary Assessor Summary Recommendation:
I recommend approval of this 351(a) BLA for ZYNLONTA (loncastuximab tesirine-lpyl). The manufacturing process is well-controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents and meets the standards recommended by FDA. The conditions used in the manufacturing process were adequately validated, and the product was consistently manufactured from multiple production runs.

II. List of Deficiencies to be Communicated:
There are no CMC-related deficiencies precluding approval of this BLA.

III. List of Post-Marketing Commitments/Requirements (draft wording for OBP PMC):
PMC #1: Develop and validate an assay to evaluate the neutralizing capacity of anti-drug antibodies (ADAs) detected in the patient samples. The assay should be capable of sensitively detecting neutralizing ADAs in the presence of loncastuximab tesirine levels that are expected to be present in serum at the time of patient sampling. Appropriately bank samples from ongoing clinical trials to evaluate and correlate neutralizing antibodies (nAbs) in all confirmed ADA-positive samples using the validated assay with safety and efficacy of loncastuximab tesirine.

IV. Assessment of Common Technical Document- Quality Module 1
A. Environmental Assessment of Claim of Categorical Exclusion:
ADCT claims a categorical exclusion per 21 CFR 25.31(c) from the environmental assessment requirements of 21 CFR 25.20. Approval of this BLA will increase the use of substances that occur naturally in the environment, but the action does not alter significantly the concentration or distribution of the substances, their metabolites, or degradation products in the environment. The request for categorical exclusion is acceptable.

V. Primary Container Labeling Assessment:
Assessed by James Barlow. A separate assessment is uploaded in Panorama.

VI. Assessment of Common Technical Document- Quality Module 3.2:
The assessment of Module 3.2 is included in this assessment memorandum.

VII. Assessment of Immunogenicity Assays- Module 5.3.1.4
The loncastuximab tesirine tiered immunogenicity testing strategy aligns with the current FDA guidance regarding immunogenicity. Patient samples were tested using adequately validated screening, confirmation, and titer assays. Anti-drug antibodies (ADAs) were not characterized or assessed for neutralizing activity as the characterization and neutralizing antibody (NAb) assays were not submitted to the application during the BLA assessment cycle. The BLA assessment team concluded that a validated NAb was not necessary for approval of the BLA as no patients were found to have treatment-emergent ADAs in the pivotal clinical study. As a validated NAb assay may be required for future clinical NAb assessment, validation of the NAb assay is agreed with the Applicant as PMC #1.

EDR: BLA 761196

Unless otherwise noted, figures and tables in the assessment are adapted or copied directly from the submission. Some of the figures and tables in the submission were updated during the assessment cycle, the assessment contains only the updated final versions. Assessor comments are distinguished by use of italic font.

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Description of Drug Substance and Drug Product

Clinical information summary

Note that the following is based on the information provided in the original submission and may not reflect modifications proposed during the BLA assessment cycle.

Non-Hodgkin lymphoma (NHL) is a diverse group of hematologic malignancies arising from precursor and mature B-, T-, and natural killer cells. Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma and accounts for ~32.5% of NHL. Approximately 25% of DLBCL patients in the US are diagnosed with localized or limited stage disease and typically have a more favorable prognosis, while approximately 75% of DLBCL patients present with advanced stage disease associated with B-symptoms or bulky disease (≥ 10 cm). Patients with advanced disease are treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Approximately 60% of DLBCL patients will be cured, ~10 – 15% of patients will exhibit primary refractory disease (non-responsive or release within three months of therapy), and ~20 – 25% of patients relapse, usually within the first two years following initial response. Current treatments for relapsed or refractory (R/R) DLBCL include salvage therapy, including high-dose chemotherapy and autologous stem cell transplant. Although this is an effective treatment for DLBCL patients with chemotherapy-sensitive relapse, over half of patients will not have long-term disease control. Although more recent therapies such as CD19-targeting chimeric antigen receptor (CAR) T-cell therapies (YESCARTA™ and KYMRIAH™), the antibody-drug conjugate polatuzumab vedotin (POLIVY™) targeting CD79b in combination with bendamustine and rituximab, the nuclear transport inhibitor selinexor (XPOVIO™), and the anti-CD19 monoclonal antibody (mAb) tafasitamab (MONJUVI™) in combination with lenalidomide have been approved for select R/R DLBCL patients, there remains an unmet medical need for the treatment of patients with R/R DLBCL. The Applicant believes that loncastuximab tesirine will benefit a broad, high-risk population of R/R DLBCL patients.

Loncastuximab tesirine was granted Orphan Drug designation for R/R DLBCL. The Applicant is seeking loncastuximab tesirine indication for the treatment of adult patients with R/R DLBCL including high-grade B-cell lymphoma, after at least two prior systemic therapies. The recommended loncastuximab tesirine dose is 150 μg/kg every 3 weeks (Q3W) for 2 cycles and 75 μg/kg Q3W for subsequent cycles administered as an intravenous infusion over 30 minutes (pre-medication with dexamethasone recommended).

The clinical study to demonstrate efficacy is the pivotal trial ADCT-402-201, an open-label, single arm Phase 2 trial (on-going) in patients with R/R DLBCL, conducted in Europe and in the US. Additional supportive safety and efficacy data for loncastuximab tesirine monotherapy was provided by ADCT-402-101, a Phase 1, open-label dose-escalation and expansion trial in patients with R/R B-cell NHL, including patients with R/R DLBCL. Additional supportive safety data was obtained from ADCT-402-102, a Phase 1, open-label, dose-escalation and expansion trial of loncastuximab tesirine in patients with R/R B-cell acute lymphoblastic leukemia (B-ALL); ADCT-402-103, a Phase 1/2, open-label, dose-escalation and expansion trial of loncastuximab tesirine in combination with ibrutinib in patients with R/R DLBCL or R/R mantel cell lymphoma (MCL); and ADCT-402-104, a Phase 1, open-label dose-escalation and expansion trial of loncastuximab tesirine in combination with durvalumab in patients with R/R DLBCL, MCL, or follicular lymphoma (FL). *The following table summarizes the results of the loncastuximab tesirine efficacy data (prepared by the assessor based on data from the submission):*

Clinical study	Efficacy endpoint (95% CI)						
	ORR	Median TTR	Median DoR	CRR	Median RFS	Median PFS	Median OS
ADCT-402-201 (n = 145) 150 μg/kg Q3W for 2 cycles, then 75 μg/kg Q3W	48.3% (39.9, 56.7)	41.0 days (35, 247)	10.25 mo. (6.87, NE)	24.1% (17.4, 31.9)	13.37 mo. (10.25, NE)	4.93 mo. (2.89, 8.31)	9.92 mo. (6.74, 11.47)
ADCT-402-101 (n = 139) All doses combined (15 – 200 μg/kg)	42.3% (33.9, 51.1)	43.0 days (31, 323)	4.47 mo. (3.94, 9.46)	23.4% (NA)	ND	2.83 mo. (1.91, 3.75)	7.46 mo. (5.95, 9.79)

ORR = overall response rate; TTR = time to tumor response; DoR = duration of response; CRR = complete response/remission; RFS = relapse-free survival; PFS = progression-free survival; OS = overall survival; NE = not estimable; ND = not done

The Applicant reports that only one out of 328 (0.305%) patients tested positive for anti-drug antibodies (ADAs) post-dose, with very low $\log_2$ titer (< 1). The presence of ADAs had no significant impact on the PK, efficacy, or safety. The most common treatment-emergent adverse events (TEAEs) were fatigue, GGT increase, neutropenia, anemia, nausea, thrombocytopenia, peripheral edema, cough, rash, ALP increase, pyrexia, constipation, decreased appetite, dyspnea, AST increase, diarrhea, ALT increase, vomiting, hypokalemia, pleural effusion, abdominal pain, pruritis, and hypomagnesemia and hypophosphatemia. The terminal elimination half-life of loncastuximab tesirine was determined to be 14.6 days (cycle 1) and 20.6 days (cycle 5).

Assessor's Comment: *The proposed proprietary name in the original submission was ZYNLONTA™. However, the Applicant was notified by the Agency that the proposed name was unacceptable because it was similar to the proprietary name for a product currently under assessment. The Applicant then proposed the proprietary name* (b) (4) *however, during the BLA assessment cycle, the Applicant was advised to submit a request for proprietary name assessment for ZYNLONTA. The proprietary name assessment was on-going on the date of this assessment. The clinical assessment team also recommended that the indication proposed by the Applicant to be changed to treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, high grade B-cell lymphoma, and DLBCL airing from follicular lymphoma.*

In the Application Orientation Meeting (AOM), the Applicant clarified that loncastuximab tesirine from manufacturing Process B was primarily used in the pivotal trial ADCT-402-201 (110/145 patients). Based on the information in the submission, loncastuximab tesirine from manufacturing Process A was also used in the pivotal trial.

As loncastuximab tesirine is an antibody-drug conjugate (ADC), this assessment covers the product quality (CMC) aspects of loncastuximab mAb intermediate, loncastuximab tesirine DS and DP, while the drug-linker intermediate, SG3249, and relevant aspects for the DS and DP are assessed by ONDP. The microbiological and facility assessments are performed by OPMA.

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IMMUNOGENICITY ASSAYS

The information source sections are denoted in [ ] in eCTD Module 5.

Immunogenicity Risk Assessment [5.3.5.3.2.1]

To assess the immunogenicity risk of loncastuximab tesirine, the Applicant assessed the intrinsic product-specific immunogenic potential of loncastuximab tesirine (e.g., mAb humanization, ADC structure/neoepitopes, cross-reactivity with endogenous proteins), product quality attributes (e.g., particulates, process- and product-related impurities), systems biology (e.g., CD19 expression/function, loncastuximab tesirine MoA), and patient-related factors (e.g., immunologic status and competence of the patient, route of administration/dose/frequency of administration, immune tolerance, premedication and supportive care). Based on this risk assessment and results of immunogenicity testing in the clinical trials, the Applicant deemed the immunogenicity risk of loncastuximab tesirine to be low.

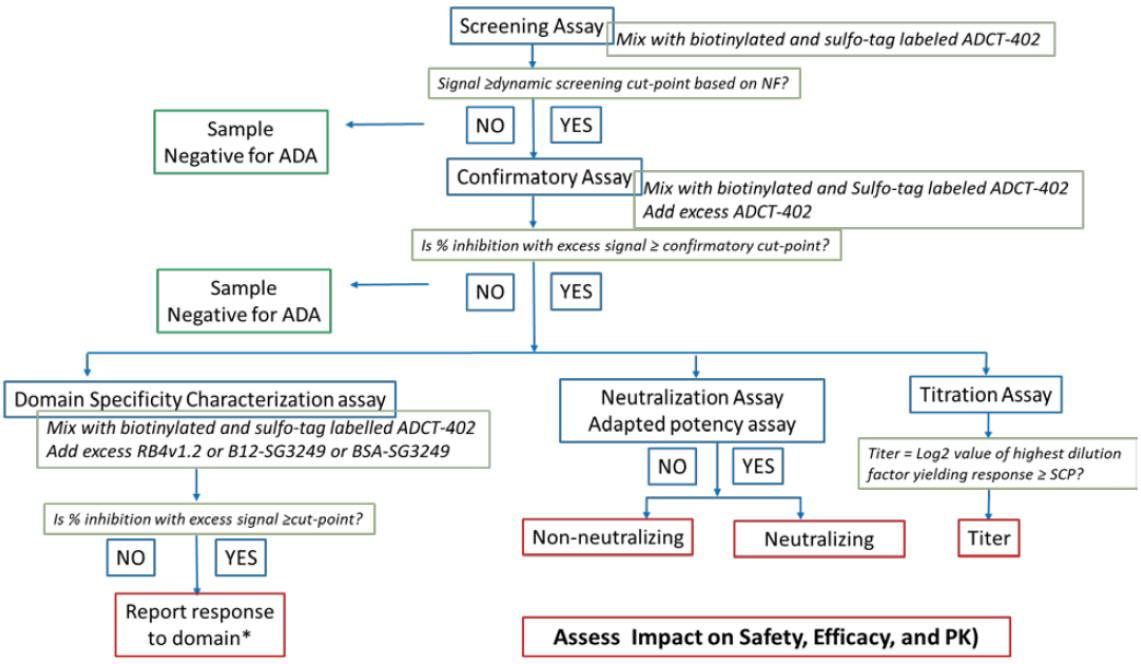
***Assessor's Comments**: We agree with the Applicant's conclusion that the immunogenicity risk with loncastuximab tesirine is low. Patients being treated with loncastuximab tesirine are likely to be heavily treated and immunosuppressed. Patients being treated with loncastuximab tesirine are also premedicated with dexamethasone, and thus, immune responses including ADA formation are likely to be reduced.*

Note that CD19 is not shed into circulation, and thus, is not expected to impact the immunogenicity assays.

Rationale for Bioanalytical Strategy [5.3.5.3.2.2]

The Applicant implemented a tiered immunogenicity testing strategy to evaluate ADAs against loncastuximab tesirine. The strategy included the evaluation of ADAs using validated screening and confirmatory assays with titer evaluation, followed by characterization and evaluation of neutralizing capacity as needed (Figure 4).

Figure 4 Anti-drug Antibody Tiered Immunogenicity Testing Strategy



Assessor's Comments: *The loncastuximab tesirine immunogenicity testing strategy aligns with the current FDA guidance regarding immunogenicity. However, the Applicant has not validated the characterization and NAb assays (described in 5.3.5.3 of the submission), and thus, patient samples were not tested in these assays. After discussing the need of a validated NAb assay with the BLA assessment team, it was concluded that the NAb assay was not needed because no treatment-emergent ADAs were observed in the pivotal clinical study. Thus, we recommended and discussed with the BLA assessment team to perform validation of these assays as part of PMC on clinical NAb assessment.*

Overview of Methods [5.3.5.3.3.1]

The screening, confirmation, and titer assays were validated at (b) (4) (b) (4). All ADA analyses for clinical studies ADCT-402-101, ADCT-402-102, and ADCT-402-201 were run at (b) (4) using the validated methods. The method validation report was included in 5.3.1.4 (Report #AHD486EL-154683-F and Amendment No. 01) and the method performance reports for the clinical studies were provided in 5.3.1.4 (Report #AHD683EL-157443-E and AHD683EL-157443-F) and 5.3.5.2 (Report #AHC405EL-174063-C).

Assessor's Comments: *The electrochemiluminescence immunoassay (ECLIA) described below was used for the screening, confirmation, and titer assays. The same assays were used to evaluate the patient samples for clinical studies ADCT-402-101, ADCT-402-102, and ADCT-402-201, thus, a single validation report was submitted.*

ADA Assay Format [5.3.5.3.3.2.2]

The ADA assay (ECLIA) is a bridging assay. Briefly on the screening assay, the samples are diluted with Superblock T20 (TBS) blocking buffer (1:2) and the antibody complexes are dissociated with acetic acid (1:5). The acidified samples are neutralized with a master mixture of Trizma base, biotinylated loncastuximab tesirine, and sulfo-tagged loncastuximab tesirine (1:4). The minimal required dilution (MRD) is 1:40. The mixtures are transferred to a streptavidin-coated MSD plate and incubated. After incubation, the streptavidin-coated plate is washed, MSD read buffer is added, and the plate is read (ECL response) on the MSD Quickplex. Samples with ECL responses equal to or above the screen cut-point (SCP) are scored as positive and any values below the SCP are scored as negative. Positive scored samples (including pre-dose) are further tested in a confirmation assay.

For the confirmation assay, a master mix that includes loncastuximab tesirine RS at final concentration of 100 μg/mL is also included. Samples with ECL response reduction equal to or greater than the confirmatory cut-point (CCP) in the presence of loncastuximab tesirine compared to absence of loncastuximab tesirine are confirmed positive. Samples with ECL response reduction lower than the CCP are not confirmed positive (i.e., negative). Confirmed positive samples are further tested in a titration assay.

For the titration assay, the SCP is used to determine ADA titer when a sample is serially diluted in drug naïve pooled human serum. The sample is diluted in a series of 2-fold dilution steps (at least 4 dilution steps), until negative scoring of the sample is achieved. The titer is calculated as a $\log_2$ value of the highest dilution factor yielding a relative response above the SCP (still scoring positive).

For routine testing of the assays, each study sample and quality control (QC) sample is analyzed in duplicate. The QCs include a neg-QC (naïve pooled human serum), low-QC (25 ng/mL, pAb against loncastuximab), and high-QC (5000 ng/mL, pAb against loncastuximab). Three sets of QCs are implemented per run (a run can contain several plates). The acceptance criteria for the assays (system suitability) must be met:

- For study samples:
  - CV of duplicates ≤ 20.0% (no criteria applied for samples for which the mean response is below the mean response of neg-QC samples per plate).
- For runs:
  - Per QC level, rejection of 1 out of 3 QC samples based on CV of duplicates is allowed; at least one positive QC (low or high) should be accepted preceding the study samples and one after the study samples.
- For QCs without drug:
  - Neg-QC CV of duplicates ≤ 20.0%,
  - Low-QC response ≥ SCP,
  - High-QC response > SCP.
- For QCs with drug:
  - Neg-QC signal reduction < CCP,
  - Low-QC signal reduction ≥ CCP,
  - High-QC signal reduction > CCP.

Assessor's Comment: *The assays and the system suitability acceptance criteria are acceptable.*

Control of Labeled Antigen(s) [5.3.5.3.3.2.4 and Report #AHD468EL-154683]

Labeling of liquid loncastuximab tesirine with biotin or sulfo-tag was conducted by (b) (4). Labeling of lyophilized loncastuximab tesirine was conducted by the Applicant in a similar manner, however, the storage buffer was changed from PBS to 30 mM histidine, 175 mM sucrose buffer at pH 6 (allows for storage at -60°C). For clinical studies ADCT-402-101 and ADCT-402-102 the liquid loncastuximab DP was used for labeling and validation of the assays. For clinical study ADCT-402-201 liquid DP and lyophilized DP were used for labeling. Bridging of newly labeled materials using the liquid and/or lyophilized loncastuximab tesirine DP was performed by running the old and new batch materials on the same plate and analyzing 3 sets of QC samples (with and without drug).

Assessor's Comment: *The labeled loncastuximab tesirine materials used to analyze the patient samples for the clinical studies are acceptable. The bridging results support no difference between labeling of the liquid and lyophilized DP.*

Negative Control Matrix [5.3.5.3.3.2.5 and Report #AHD468EL-154683]

The source of the naïve pooled human serum (blank matrix) to prepare the neg-QC sample used for validation was a serum pool from 10 healthy individuals. Based on this neg-QC sample the normalization factor (NF) was defined as 1.25. For clinical study ADCT-402-101 this neg-QC was used initially and during the ADA analyses for clinical studies ADCT-402-101, ADCT-402-102, and ADCT-402-201, three new blank matrices were introduced and new neg-QC samples were made. A new NF was established using three runs in which the old and the new blank matrix pools were analyzed. The mean ratio between the responses of the two pools was used to calculate the new NF (Table 4).

Table 4 Information on Negative Control Matrix

Pooled blank matrix ID*	# individuals	Normalization factor	validation	ADCT-402-101	ADCT-402-102	ADCT-402-201
16-0642	10	1.25	√	√		
16-2366	3	1.2		√	√	
18-1262	3	1.15		√	√	√
19-0382	6	1.16		√		√

During validation, 10 individual samples of patients with ALL and 10 individual samples of patients with NHL (drug naïve) were also evaluated for matrix variability and matrix interference. Although some of the ALL and NHL samples tested positive, the degree of matrix variability was deemed acceptable by the Applicant.

Assessor's Comments: *The Applicant used the NFs in Table 4 to determine the SCP for runs used to analyze patient samples and are discussed further below. One out of 10 and 3 out of 10 ALL and NHL patient serum samples, respectively, tested positive in the screening assay. However, only one ALL patient serum sample was confirmed positive. The signal for this sample (ECL response = 1012) was significantly higher than the SCP of 192. However, the signal for the NHL samples that screened positive were close to the SCPs. Based on this limited data, it appears that the sample matrix from patients with ALL and NHL have potentially higher signal then the sample matrix from healthy individuals thus using the latter will be the worst-case for false positivity. While this will result in testing of more samples in the confirmation assay, the confirmation assay is unlikely to be significantly impacted by the matrix differences, thus, the immunogenicity rates for the clinical studies should not be impacted.*

Positive Control Reagents [5.3.5.3.3.2.6 and Report #AHD468EL-154683]

The positive control for the ADA assay is an affinity purified rabbit pAb generated against loncastuximab (batch B114-0313). Mouse mAbs against loncastuximab (hybridoma clones 31-1-15 and 26-5-3) and the SG3249 drug-linker (hybridoma clone 14B3-B7) were also used in the validation of the assay to show that these antibodies, with different binding sites and/or kinetics, provide low/comparable sensitivities to the pAb.

Assessor's Comments: *The positive control antibody for the ADA assay is acceptable. The sensitivity of the mouse mAbs against loncastuximab and the drug-linker was determined as described for the pAb below (serial dilution until negative scoring is achieved). The data shows that the ADA assay is able to detect different ADAs against the mAb and drug-linker portions of loncastuximab tesirine with acceptable sensitivity (see below*).

Justification of Competing Antigen Concentration for Confirmation Assay [5.3.5.3.3.2.7]

To determine drug tolerance of the ADA assay (*see below*), a dilution series of loncastuximab tesirine starting at 100 μg/mL was tested to determine inhibition of the signal for the low-QC (25.0 ng/mL). The excess 100 μg/mL loncastuximab tesirine was found to block the signal of the low-QC below the SCP in the three runs used to evaluate drug tolerance.

Assessor's Comments: *The Applicant did not assess the inhibition of the signal for high-QC (5000 ng/mL) as performed for the low-QC by diluting the loncastuximab tesirine starting at 100 μg/mL. However, the validation runs for the confirmation assay show that 100 μg/mL excess loncastuximab*

tesirine consistently inhibits > 95% of the high-QC signal. Thus, the 100 μg/mL excess loncastuximab tesirine concentration is acceptable for the confirmation assay.

Choice of QC Concentrations [5.3.5.3.3.2.9]

The neg-QC contains blank matrix and is used to set the SCP based on the NF. The low-QC was chosen at a level that produced a signal that could be reproducible seen above the SCP. For the high-QC, a level was chosen that produced a signal on the upper end of linear response of the assay.

Assessor's Comments: *The Applicant acknowledges that the low-QC does not meet the current FDA guidance recommendations of using a low-QC concentration leading to a rejection of an assay run of 1%. However, the Applicant justifies that the low-QC at 25 ng/mL supports the sensitivity requirement of ≤ 100 ng/mL and the concentration and signal is close to the sensitivity level of the assay. The QC sample concentrations are reasonable.*

Selectivity: Interference from Matrix, Drug, and Target [5.3.5.3.3.2.10 and Report #AHD468EL-154683]

As described for the blank matrix, the matrix variability of 10 individual serum matrices each of healthy individual, ALL patients, and NHL patients was deemed to be acceptable even though some of the ALL and NHL patient samples screened positive. Therefore, pools of serum from healthy individuals are used for routine testing.

For validation of the ADA assay, drug interference (drug tolerance) was determined using the low-QC and adding a series of loncastuximab tesirine starting at 100 μg/mL and performing 2-fold serial dilutions until positive scoring was achieved using the SCP. The number of runs used was three runs with a single replicate per run. Drug tolerance was set at the highest drug concentration added to the samples which resulted in a positive score in all three runs. The drug tolerance was determined to be 12.5 μg/mL loncastuximab tesirine. The Applicant acknowledges that current FDA guidance recommends using at least six independent determinations for establishing drug interference. Because the drug tolerance was considerably higher than trough drugs levels (most ADA samples total Ab measurements ≤ 2.20 μg/mL), the Applicant deemed the drug tolerance based on three runs to be acceptable.

Since CD19 is not shed into circulation, soluble CD19 levels were not measured and selectivity for soluble CD19 was not included in validation.

Assessor's Comments: *The clinical pharmacology assessment team clarified that the maximum total Ab C_{trough} in cycle 2 in the 200 μg/kg Q3W cohort (cohort in which highest C_{trough} was expected) was 2.20 μg/mL for clinical study ADCT-402-101. No C_{trough} measurements were provided in later cycles for the study. In study ADCT-402-201, the maximum total Ab C_{trough} in cycle 2 (after the second 150 μg/kg dose, time at which highest C_{trough} was expected) was 2.3 mg/mL. Thus, no interference by loncastuximab tesirine in detecting ADAs in the ADA assay is expected, including low levels of ADAs which is represented by the low-QC. This result is expected as the typical doses of ADCs are significantly lower than those of most naked mAbs. The determination of drug interference using three runs is acceptable as the drug tolerance is significantly higher than the drug trough levels and the results of the three runs are comparable.*

The Applicant did not assess selectivity in hemolyzed or lipemic samples. However, a number of clinical samples were hemolyzed and scored as either negative or positive in the screening assay, but were negative in the confirmation assay. This observation suggests that there is likely no conclusion-defining matrix effect in these samples as there is no correlation between being a hemolyzed sample and scoring in the screening or confirmation assays.

Sensitivity [5.3.5.3.3.2.11 and Report #AHD468EL-154683]
For validation of the ADA assay, sensitivity was determined by spiking high-QC (5000 ng/mL) into blank matrix and diluting 2-fold until negative scoring was achieved using the SCP. The number of runs used was three runs with a single replicate per run. The lowest antibody concentration yielding a result ≥ SCP in all three runs was selected as LOD and indicated as the sensitivity. The sensitivity was determined to be 9.77 ng/mL. The Applicant acknowledges that current FDA guidance recommends using at least six independent determinations for establishing sensitivity. Because the sensitivity was well below the recommended 100 ng/mL, the Applicant deemed the sensitivity based on three runs to be acceptable. In addition, the Applicant did not assess sensitivity in the presence of the expected concentration of onboard drug because drug tolerance for the low-QC (25 ng/mL) was shown to be 12.5 µg/mL and it is expected that detection of the pAb against loncastuximab at 9.77 ng/mL will also not be significantly impacted by expected onboard concentrations of loncastuximab tesirine (≤ 2.20 µg/mL). Using the same procedure and one run, the sensitivities for mouse mAbs generated against loncastuximab and the drug linker were determined to be 39.1 ng/mL, 4.88 ng/mL, and ≤ 2.44 ng/mL for clones 31-1-15, 26-5-3, and 14B3-B7, respectively.
Assessor's Comments: *The sensitivity of the ADA assay is acceptable per FDA guidance (≤ 100 ng/mL). The determination of sensitivity using three runs is acceptable as the results of the three runs are comparable.*

Prozone (Hook Effect) [Report #AHD468EL-154683]
For validation of the ADA assay, prozone (hook effect) was evaluated by spiking high-QC (5000 ng/mL) into blank matrix and diluting 2-fold until negative scoring was achieved using the SCP. A single replicate in one run was used. No prozone was detected [all relative response values of the highest samples were ≥ 80.0% of the response values of their respective preceding (lower) samples].
Assessor's Comments: *Although, no prozone was observed, there does appear to be a plateau of the ECL signal at the highest two concentrations tested (2500 – 5000 ng/mL). This does not impact validation and should not impact testing for ADAs in clinical samples.*

Establishment and Validity of Assay Cut-points [5.3.5.3.3.2.12 and Report #AHD468EL-154683]
In the validation of the ADA assay, the determination of the SCP was based on 50 individual human (drug naïve) serum samples run in six runs on four different days by two technicians. For each run, a SCP was determined from the signal of the non-specific background based on the 95% upper confidence limit to allow the identification of false-positives. The Shapiro-Wilk test was performed to evaluate normality. The untransformed data set was not normally distributed. The data was log-transformed and outliers [low outliers = quartile (Q)1 – 1.5*(Q3 – Q1) and high outliers = Q3 + 1.5*(Q3 – Q1)] were removed, however, the data for 2/6 runs was not normally distributed. Therefore, the SCP was determined for each run using the 95th percentile (non-parametric method). The NF was calculated per run by correcting the SCP by the mean ECL response of the neg-QC sample. Because the means (one-way ANOVA) and variances (Levene's test) between the runs differed, a dynamic SCP was used. As the mean NF was 1.25 with CV of 6.1%, the mean NF was used to calculate the plate-specific SCP, defined as neg-QC*NF. If a new naïve pooled human serum (blank matrix) was used for neg-QC, a new NF was established (discussed above).
To determine the CCP, the 50 individual human serum samples were also spiked with 100 µg/mL loncastuximab tesirine. The mean ECL response was used to calculate the percent signal inhibition using three runs on two different days by two technicians. The CCP was determined from the percentage

signal reduction based on a 99.9% upper confidence limit to allow the identification of false-positives. After outlier removal, the untransformed data set was normally distributed. The CCP of a run was determined from percent signal reduction based on a 99.9% upper confidence limit (mean + 3.09*SD). The CCP calculated by taking the mean of the three run CCPs was 30.7% (CV = 2.8%) signal reduction. To validate the ADA assay for determining titer, 2-fold serial dilution of samples until negative scoring is achieved was demonstrated (determination of sensitivity). The titers [expressed as $\log_2$ value of the highest dilution factor yielding a response ≥ SCP (scoring positive)] in the validation runs were 9/10 (512/1024 dilution).

Assessor's Comments: *Although the Applicant has stated that a dynamic SCP is used in the Integrated Summary of Immunogenicity (ISI) in 5.3.5.3, it appears that this is a misnomer and a floating SCP with a correction factor is used. Typically, a dynamic SCP includes running individual naïve human serum samples on each plate and a SCP is determined based on these samples for each plate. However, this is not performed for the screening assay. The Applicant uses the NF determined in validation with a correction factor when the blank matrix (used for neg-QC and dilution of samples for titer assay) is changed. As shown in Table 4 above, three additional blank matrix pools were used in the runs used to analyze patient samples for clinical studies ADCT-402-101, ADCT-402-102, and ADCT-402-201. The Applicant established the new NF for a new blank matrix by running the old (validation) and new blank matrices in three runs. The mean ratio between the responses was used to calculate the new NF (=mean old pool ECL response/mean new pool ECL response*old NF). Although this approach is unorthodox, it appears to be a conservative approach as the new NFs are all below the old NF, and thus, the consequence would likely be a higher false-positive rate for the screening assay. A higher than expected false-positive rate was observed for clinical studies ADCT-402-101 and ADCT-402-201 (see below). The confirmation assay will confirm positivity of samples, and thus, reported immunogenicity rates for the clinical studies will not be impacted.*

The Applicant also did not confirm the SCP using pre-dose samples from the patients in the clinical samples, which may have also contributed to a higher false-positive rates in the clinical studies. Based on the evaluation of 10 individual samples from ALL and NHL patients, it appears that there may be potential for matrix differences between normal human and patient serum samples toward 'positivity' in patient samples.

Overall, the cut-points for the screening and confirmation assays, and titer determination are acceptable. There is an increased risk for higher false-positivity rates with the current screening assay, but the confirmation assay will confirm ADA-positivity in clinical samples.

Precision [Report #AHD468EL-154683]

The precision of the response (relative), scoring, and signal reduction was determined using the data from the runs used to determine the SCP and CCP for validation. The response intra-run/inter-run/total precision (% CV) was determined to be 5.1/3.7/6.3% and 6.7/4.6/8.1% for the low-QC and high-QC, respectively. The relative response intra-run/inter-run/total precision was determined to be 5.1/8.0/9.5% and 6.9/12.7/14.4% for low-QC/neg-QC ratio and high-QC/neg-QC, respectively. The signal reduction intra-run/inter-run/total precision was determined to be 7.8/2.9/8.3% and 0.4/0.1/0.4% for the low-QC and high-QC, respectively. For scoring, 100% of the low-QC and high-QC samples scored positive in both the screening and confirmation assays.

Assessor's Comment: *The intra- and inter-run precision of the ADA assay is acceptable per FDA guidance (% CV < 20).*

Stability [Report #AHD468EL-154683]

Bench-top stability of the low-QC and high-QC stored at room temperature for 24 hours was evaluated. In addition, the impact of 6 freeze/thaw cycles (-70°C or -20°C for at least 12 hr and room temperature for 2 hr) on low-QC and high-QC was evaluated. One run with three determinations was used. Samples were found to be stable after storage at room temperature for 24 hr and 6 freeze/thaw cycles compared to controls.

***Assessor's Comment*:** *The stability studies for the low-QC and high-QC are adequate.*

Results of Clinical Evaluation [5.3.5.3.4]

Patient samples from clinical studies ADCT-402-101, ADCT-402-102, and ADCT-402-201 were evaluated for ADAs (Table 9). Overall, 144/363 patients screened positive and 8/144 patients confirmed positive. Only one patient was positive for treatment-emerging (post-dose) ADAs (titer = 2). All titers were ≤ 3 (highest dilution scoring positive was ≤ 8). The Applicant also evaluated false-positives and found that false-positives were found in pre-dose and post-dose samples (Table 12).

Table 9 Summary of treated subjects, treatment regimen and ADA screening and confirmation figures by study and overall

		Clinical trials				Overall
		[1]ADCT-402-101	[2]ADCT-402-102		[3]ADCT-402-201^	
Patient number information						
part 1+2/ pivotal	# of patients treated	183	35		145	**363**
	# of patients evaluated for ADA	183	36[$]		145	**364[$]**
	# of samples evaluated for ADA	925	112[$]		687[&]	**1724[$&]**
	# of samples screened positive (% of total samples screened)	177 (19.1%)	11 (9.82%)		99 (14.4%)	**287 (16.6%)**
	# of patients screened positive	82	8		54	**144**
	# of samples confirmed positive (% of samples screened positive)	26 (14.7%)	1 (9.09%)		1 (1.01%)	**28 (9.76%)**
	# of patients confirmed positive	6	1		1	**8**
	# patients confirmed positive pre-dose (% of patients treated)	5[#] (2.73%)	1 (2.86%)		1 (0.689%)	**7**
	#patients confirmed positive and negative pre-dose (% of patients treated)	1 (0.545%)	0 (0%)		0 (0%)	**1 (0.275%)**

Table 12 False ADA Positives Provided for Pre-and Post-treatment Samples

Study	ADCT-402-101		ADCT-402-102		ADCT-402-201		Overall	
timepoint	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
# of samples false positive	31	120	2	8	24	74	57	202

Assessor's Comments: *Based on the information provided in Tables 9 and 12 above, the pre-dose screening false-positive rates for clinical studies ADCT-402-101, ADCT-402-102, and ADCT-402-201 were 16.9% (31/183), 5.6% (2/36), and 16.5% (24/145), respectively. The false-positive rates for clinical studies ADCT-402-101 and ADCT-402-201 are higher than expected for a screening assay and is likely attributed to the correction factor used for the SCP and/or the matrix factors in the pre-dose patient samples that impact the ECL response. Nonetheless, the CCP appears to be adequate, and thus, confirmation of positivity of patient samples and immunogenicity rates for the clinical studies should not be impacted.*
Overall, the ADA assay is adequate for immunogenicity testing for the clinical studies used to support approval of the BLA.
Note that the deviations reported in the validation report do not impact validation of the ADA assay.

Massod Rahimi

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PRODUCT QUALITY MICROBIOLOGY/FACILITY ASSESSMENT
Memorandum of Review to the File

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Application ID	761196/0
Submission Type	Original BLA
Drug Product Name	Loncastuximab tesirine-xxxx (Zynlonta™)
Strengths	10 mg/vial
Dosage Form	Lyophilized powder
Administration Route	Intravenous
Indication	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after at least two prior systemic therapies
Applicant Name	ADC Therapeutics SA
US License Number	2166
Application Type	BLA
Primary Reviewer	Amy Devlin, Microbiologist, Ph.D.
Secondary Reviewer	Candace Gomez-Broughton, Branch Chief, Ph.D.
Goal Date	May 21, 2021

Recommendation for Approvability:

- This BLA was reviewed from a product quality microbiology perspective and sterility assurance perspective. Approval recommendation is pending review of the following information in an addendum to the review memo:
  1. Results of rabbit pyrogen test performed on three lots of drug product demonstrating non-pyrogenicity per 21 CFR 610.13(b). Description of the method and summary results will be submitted to the BLA by April 15, 2021.
  2. Shipping qualification data, development study data, and the report for the transport verification study will be provided by end of March 2021.
- Manufacturing Facility Assessment Recommendation: Approval
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

Summary Basis of Recommendation (DP):

All sterile drug product-contact equipment and components are sterilized and depyrogenated using validated processes. The drug product is sterilized using a validated (b) (4) process (b) (4) (b) (4) (b) (4) Bioburden and endotoxin are tested during manufacture, and sterility and endotoxin are tested at release. Container closure integrity testing using a validated method is included in the stability program.

Drug Product CQA Process Risk Identification and Lifecycle Knowledge Management:

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

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original submission (0001)	08/07/2020
Original submission (0002)	09/21/2020
Response to FDA IR sent on 10/02/2020 (0003)	10/08/2020
Response to FDA IR sent 12/04/2020 (0014)	12/18/2020
Response to FDA IR sent 02/05/2021 (0024)	02/16/2021
Response to FDA IR sent 02/22/201 (0029)	03/03/2021

List of DMFs assessed (Table):

DMF #	Date Reviewed	Finding	Document Reference
(b) (4)	01/29/2020	Adequate	D (b) (4) M40R01.docx

MODULE 1

1.14 LABELING

Section 2.4 of the label indicates that Zynlonta™ should be reconstituted with 2.2 mL sterile water for injection (sWFI) and used immediately but may be stored refrigerated (2-8°C) or at room temperature (20-25°C) for up to 4 hours before dilution. Calculated dose of reconstituted Zynlonta™ should be added directly into a 50 mL 5% dextrose intravenous infusion bag. If not used immediately, diluted Zynlonta™ solution in the IV bag can be stored refrigerated (2-8°C) for up to 24 hours or at room temperature (20-25°C) for up to 8 hours. The infusion is administered using a dedicated line with either an in-line or add-on sterile 0.2 or 0.22 µm filter.

Reviewer's Comment: *Information to support the reconstitution and dilution hold times is included in section 3.2.P.2.6 of the BLA (Compatibility). The reconstitution and dilution times are supported by growth promotion data.*

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Candace Gomez-Broughton

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PRODUCT QUALITY MICROBIOLOGY/FACILITY ASSESSMENT
Memorandum of Review to the File

Application ID	BLA 761196
Submission Type	Original BLA
Drug Product Name	Zynlonta (Loncastuximab Tesirine)
Strengths	10 mg
Dosage Form	lyophilized powder
Administration Route	Intravenous (IV)
Indication	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after at least two prior systemic therapies.
Applicant Name	ADC Therapeutics SA
US License Number	2166
Application Type	351 (a)
Primary Reviewer	Bo Chi, Ph.D., CDER/OPQ/OPMA/DBM/Branch 1
Secondary Reviewer	Candace Gomez-Broughton, Ph.D., Branch Chief, CDER/OPQ/OPMA/DBM/Branch 2 Zhong Li, Ph.D., SPQA, CDER/OPQ/OPMA/DBM/Branch 1
Goal Date	5/21/2021
Review Date	3/5/2021

Recommendation for Approvability:

- Manufacturing Facility Assessment Recommendation: Approval
- This BLA was reviewed from a product quality microbiology perspective and is recommended for Approval with the following post-marketing commitment (PMC):

  Complete the qualification of endotoxin test method for the in-process (b) (4) (b) (4) samples using samples from two additional RB4v1.2 antibody lots. In addition, complete the qualification of bioburden test method for the in-process samples using samples from two additional RB4v1.2 antibody lots. Submit the method qualification data.

- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

Summary Basis of Recommendation (DS):

Overall, the process is under adequate microbial control. Microbial quality is controlled at each step of the manufacturing process (b) (4) (b) (4). Bioburden and endotoxin samples are monitored at each critical step of the manufacturing process (b) (4). Microbial control (b) (4) is continuously monitored (b) (4) and (b) (4) (b) (4) will be validated. (b) (4)

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

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) and (b) (4), proposed for RB4v1.2 monoclonal antibody (mAb) intermediate and loncastuximab tesirine DS manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management:

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

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
CMC submission (0001)	8/7/2020
Response to IR (0013)	12/16/2020
Response to IR (0027)	2/22/2021

Application Submission Background

ADC Therapeutics has submitted this Biologics License Application (BLA) for loncastuximab tesirine for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Loncastuximab tesirine (ADCT-402) is a CD19-targeted antibody-drug conjugate (ADC), with monoclonal antibody RB4v1.2 conjugated to SG3199, a cytotoxic drug, through linker SG3249. The drug substance intermediate (DSI, monoclonal antibody RB4v1.2) is manufactured at (b) (4). The drug substance (DS) and drug product (DP) are manufactured at (b) (4) (b) (4). This application contains CMC information in an eCTD format.

This review contains an assessment of the Loncastuximab tesirine drug substance intermediate and drug substance sections of the BLA from a product quality microbiology perspective.

MODULE 3.2.S

Module 3.2.S Lifecycle Management Considerations

Lifecycle considerations:	No
Post-approval inspection?	No

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Bo Chi

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Zhong Li

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