APPLICATION NUMBER:

761196Orig1s000

OTHER REVIEW(S)
1 PURPOSE OF MEMORANDUM
The Applicant submitted revised container label and carton labeling received on March 12, 2021 for Zynlonta. We reviewed the revised container label and carton labeling for Zynlonta (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.\textsuperscript{a}

2 CONCLUSION
The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

\textsuperscript{a} Iverson N. Label and Labeling Review for Zynlonta (BLA 761196). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 26. RCM No.: 2020-1658.
APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 12, 2021

Container label

Carton labeling
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/

NICOLE F IVERSON  
04/13/2021 03:08:24 PM

HINA S MEHTA  
04/14/2021 02:48:40 PM
Date: March 29, 2021

To: Jennifer Lee, PharmD  
Senior Regulatory Health Project Manager  
Division of Hematologic Malignancies 2 (DHM2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
Division of Medical Policy Programs (DMPP)

From: Ruth Mayrosh, PharmD  
Patient Labeling Reviewer  
Division of Medical Policy Programs (DMPP)

Nisha Patel, PharmD  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TRADENAME (loncastuximab tesirine-lpyl)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: BLA 761196

Applicant: ADC Therapeutics America Inc.
1 INTRODUCTION

On September 21, 2020, ADC Therapeutics America Inc. submitted for the Agency’s review an original Biologics License Application (BLA) 761196 for TRADENAME (loncastuximab tesirine-lpyl) for injection. The proposed indication for TRADENAME (loncastuximab tesirine-lpyl) for injection is for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) including high grade B-cell lymphoma, after at least two prior systemic therapies.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies 2 (DHM2) on October 29, 2020 for DMPP and OPDP to review the Applicant’s proposed Patient Package Insert (PPI) for TRADENAME (loncastuximab tesirine-lpyl) for injection.

2 MATERIAL REVIEWED

- Draft TRADENAME (loncastuximab tesirine-lpyl) for injection PPI received on September 21, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 18, 2021.
- Draft TRADENAME (loncastuximab tesirine-lpyl) for injection Prescribing Information (PI) received on September 21, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 18, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:
- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
ensured that the PPI meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.
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/s/

RUTH I MAYROSH
03/29/2021 08:15:22 AM

NISHA PATEL
03/29/2021 08:17:48 AM

BARBARA A FULLER
03/29/2021 08:23:28 AM

LASHAWN M GRIFFITHS
03/29/2021 08:31:23 AM
Memorandum

Date: March 23, 2021

To: Jennifer Lee, Regulatory Project Manager
Division of Hematologic Malignancies 2 (DHM2)

Elizabeth Everhart, Associate Director for Labeling, DHM2

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O’Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for ™ (loncastuximab tesirine-lpyl) for injection, for intravenous use

BLA: 761196

In response to DHM2’s consult request dated October 29, 2020, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the original BLA submission for ™ (loncastuximab tesirine-lpyl) for injection, for intravenous use.

Labeling: OPDP’s comments on the proposed labeling are based on the draft labeling received by electronic mail from DHM2 on March 17, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.

20 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page
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/s/

NISHA PATEL
03/23/2021 03:00:55 PM
I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study ADCT-402-201 were submitted to the Agency in support of a Biologics License Application (BLA 761196) for loncastuximab tesirine (ADCT-402), proposed for treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma including high grade B-cell lymphoma, after at least two prior systemic therapies. Two clinical investigator sites (Paolo Caimi, M.D. and Brad Kahl, M.D.) and sponsor (ADC Therapeutics America, Inc.) were inspected, in support of BLA 761196.

Based on these inspections, the conduct of the above Study ADCT-402-201 appears to be adequate. The study data derived from Drs. Caimi’s and Kahl’s clinical investigator sites, plus the sponsor are considered reliable. The study data submitted to the Agency appear acceptable in support of this BLA and the proposed indication.
II. **BACKGROUND**

Loncastuximab tesirine is a CD19-targeted antibody-drug conjugate (ADC), consisting of a humanized IgG1 kappa monoclonal antibody specific for human CD19 (RB4v1.2 monoclonal antibody), conjugated to SG3199, a pyrrolobenzodiazepine dimer cytotoxic drug, through a protease-cleavable valine-alanine linker (SG3249 drug linker).

The data presented in this application is to support treatment with loncastuximab tesirine in adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL), who are unable to tolerate treatment, or whose disease have failed to respond to therapy.

A single study, Study ADCT-402-201, in part, will form the basis for the regulatory decision-making process for this application.

**Study ADCT-402-201**

Study ADCT-402-201 was an ongoing Phase 2, multicenter, open-label, single-arm study of the efficacy and safety of loncastuximab tesirine used as monotherapy in patients with relapsed or refractory DLBCL.

The treatment period started on the date a patient received the first dose of loncastuximab tesirine and continued until the date of discontinuation from treatment. A treatment cycle was defined as three weeks. Loncastuximab tesirine was administered as an intravenous infusion over 30 minutes on Day 1 of each cycle. Patients received 150 $\mu$g/kg once every 3 weeks for 2 cycles, then 75 $\mu$g/kg once every three weeks for subsequent cycles.

The primary objective was to evaluate the efficacy of single agent loncastuximab tesirine in patients with relapsed or refractory DLBCL.

The primary efficacy endpoint was overall response rate, according to the 2014 Lugano classification as determined by central review in all-treated patients. The endpoint was defined as the proportion of patients with a best overall response of complete response or partial response.

The study was conducted at 37 sites in 4 countries (USA: 24 sites, UK: 7 sites, Italy: 5 sites, and Switzerland: 1 site). The date of first patient enrollment was August 1, 2018. The data cutoff date for the submission was April 6, 2020. The study is ongoing.

DHM2 requested inspection two U.S. high patient accrual enrollment sites, and inspection of the sponsor’s site, to assess, in part, sponsor conduct of the clinical trial Study ADCT-402-201.

III. **RESULTS (by site)**

1. **Paolo Caimi, M.D. / Site 7**
   University Hospitals Cleveland Medical Center
   11100 Euclid Avenue
   Cleveland, OH 44106
Inspection dates: December 14 to 21, 2020

A total of 12 study subjects were screened and 10 study subjects were enrolled and received study treatment at the site for Study ADCT-402-201. All 10 study subjects who received study treatment discontinued due to the following reasons: five patients developed progressive disease, four study patients developed unacceptable drug toxicity and a single study subject withdrew from the study. Three patients are still in long-term follow-up for the study.

Records reviewed included but were not limited to: investigator agreements, financial disclosure forms, Institutional Review Board (IRB) approvals and documentation, delegation log, screening and enrollment log, monitoring log and monitoring reports, electronic case report forms (eCRFs), subject source records, electrocardiography records, test article control records, adverse event/serious adverse event documentation, and informed consent documentation.

Source records for the 10 enrolled study patients at the site were reviewed and compared with the Applicant’s submitted data listings for the site. All other medical records are electronic and are found in the electronic medical record or electronic data capture system.

The primary efficacy endpoint data were verified against the data line listings. No discrepancies were noted. There was no under-reporting of serious adverse events.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

2. Brad Kahl, M.D. / Site 6
Washington University School of Medicine
660 South Euclid Avenue, # 8056
St. Louis, MO 63110
Inspection dates: January 5 to 8, 2021

There were 11 study subjects screened and seven patients were enrolled at the site for Study ADCT-402-201. These seven patients received study treatment. Five study subjects died due to disease progression or relapse during active treatment. Two study subjects are still in follow-up.

The following regulatory documents were assessed: IRB approval letters and correspondence, monitoring reports, informed consent forms, subject medical records, financial disclosure reports, case report forms, subject questionnaires and diaries, dosing records, PET (positron emission tomography) scans, independent reviewer imaging, site signature and responsibility logs, and site training documentation. All subjects were consented prior to screening for the study. All the enrolled subjects’ records were audited for eligibility, protocol adherence and adverse event reporting.
Source records at the site for all enrolled study patients were examined and verifiable for primary and secondary endpoint data against the data line listings. There was no evidence of under-reporting of adverse events or protocol deviations. No discrepancies were noted.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

3. **ADC Therapeutics America, Inc.**  
   430 Mountain Ave., Suite 404  
   Murray Hill, NJ 07974

   Inspection dates: December 15 to 22, 2020

   The inspection assessed ADC Therapeutics America’s responsibilities for oversight of Study ADCT-402-201.

   The inspection included a review of the organizational charts, contract agreements, validation documents, serious adverse event reporting, monitoring plans, monitoring visit reports, standard operating procedures, selection of monitors and clinical investigators, training, test article accountability records, temperature excursions, Form FDA-1572s (Statement of Investigator), financial disclosure forms, audit trails, electrocardiograms and charters.

   In general, study procedures, recordkeeping and reporting procedures were adequate. The sponsor’s oversight for Study ADCT-402-201 were found to be appropriate. No underreporting of significant adverse events (SAEs) to the Agency was noted.

   There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

   **{See appended electronic signature page}**
   Anthony Orencia, M.D., Ph.D.  
   Good Clinical Practice Assessment Branch  
   Division of Clinical Compliance Evaluation  
   Office of Scientific Investigations

CONCURRENCE:

   **{See appended electronic signature page}**
   Min Lu, M.D., M.P.H.  
   Good Clinical Practice Assessment Branch  
   Division of Clinical Compliance Evaluation  
   Office of Scientific Investigations

Reference ID: 4762392
CONCURRENCE:

(See appended electronic signature page)
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
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/

ANTHONY J ORENCIA
03/15/2021 02:48:00 PM

MIN LU
03/15/2021 02:54:44 PM

KASSA AYALEW
03/15/2021 03:09:27 PM
**LABEL AND LABELING REVIEW**
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

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<tbody>
<tr>
<td>Requesting Office or Division:</td>
<td>Division of Hematologic Malignancies 2 (DHM 2)</td>
</tr>
<tr>
<td>Application Type and Number:</td>
<td>BLA 761196</td>
</tr>
<tr>
<td>Product Name, Dosage Form, and Strength:</td>
<td>Loncastuximab tesirine-xxxx* for Injection, 10 mg/vial</td>
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<tr>
<td>Rx or OTC:</td>
<td>Prescription (Rx)</td>
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<tr>
<td>Applicant/Sponsor Name:</td>
<td>ADC Therapeutics SA</td>
</tr>
<tr>
<td>FDA Received Date:</td>
<td>September 21, 2020, December 3, 2020, and January 4, 2021</td>
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<td>OSE RCM #:</td>
<td>2020-1658</td>
</tr>
<tr>
<td>DMEPA Safety Evaluator:</td>
<td>Nicole Iverson, PharmD, BCPS</td>
</tr>
<tr>
<td>DMEPA Team Leader:</td>
<td>Hina Mehta, PharmD</td>
</tr>
</tbody>
</table>

* The proposed proprietary name has not been determined. In addition, the proper name for has not yet been determined; therefore, “loncastuximab tesirine -xxxx” is used throughout this review as the proper name for this product.
1 REASON FOR REVIEW
As part of the approval process for BLA 761196 loncastuximab tesirine-xxxx for Injection, 10 mg/vial, this review evaluates the proposed container label, carton labeling, Prescribing Information (PI) and Patient Information for areas that may lead to medication errors.

2 MATERIALS REVIEWED
We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
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<td>Product Information/Prescribing Information</td>
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<td>Previous DMEPA Reviews</td>
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<td>Human Factors Study</td>
<td>C – N/A</td>
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<td>ISMP Newsletters*</td>
<td>D – N/A</td>
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<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E – N/A</td>
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<tr>
<td>Other</td>
<td>F – N/A</td>
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<tr>
<td>Labels and Labeling</td>
<td>G</td>
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</table>

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED
ADC Therapeutics SA submitted a 351(a) application to obtain marketing approval of loncastuximab tesirine-xxxx for Injection. Loncastuximab tesirine-xxxx is proposed for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) including high grade B-cell lymphoma, after at least two prior systemic therapies.

We performed a risk assessment of the proposed container label, carton labeling, PI and Patient Information for loncastuximab tesirine-xxxx for Injection to determine whether there are significant concerns in terms of safety related to preventable medication errors. We identified areas of the proposed label and labeling that could be revised to improve clarity and readability of important information. For the Division, we note that the PI lacks clarity in the reconstitution instructions, dilution instructions, administration instructions, dosage form,
inconsistency in the numeric dose and strength, how supplied and storage information. We also note the use of abbreviations and symbols, the numeric doses and strength are presented in multiple units of measure, and the nonproprietary name suffix placeholder, “-xxxx” is missing. We also note the Patient Information uses the incorrect dosage form and the nonproprietary name suffix placeholder, “-xxxx” is missing. For the Applicant, we note the inconsistency in the numeric dose and strength, storage information lacks prominence, the format for the expiration date is not defined, prominence of the Rx only statement, and the recommended dosage statement is missing. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS
We identified areas in the proposed container label, carton labeling, PI and Patient Information, that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for ADC Therapeutics SA to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCES 2 (DHM 2)

A. Highlights of Prescribing Information

1. As currently presented the dosage form in the title is incorrect. We recommend including the correct dosage form, “for injection”. Therefore, revise the statement, to “(loncastuximab tesirine-xxxx) for injection, for intravenous use”.

2. Dosage and Administration Section

   a. We recommend revising the first bullet for clarity as currently as follows:

      “is an intravenous infusion administered over 30 minutes on Day 1 of each cycle (every 3 weeks). The recommended dosage is:”.

   b. The frequency of administration is expressed with the abbreviation, “Q3W”. Certain abbreviations should not be used in the Prescribing Information because they are frequently misinterpreted and can lead to medication errors that may result in patient harm. We recommend replacing the abbreviation, "Q3W" with the intended meaning, "every 3 weeks".
c. Numeric doses and strength are presented in multiple units of measure. For example, the recommended dosage is presented in units of "\frac{mg}{kg}" and the strength is presented in units of "mg". Developing a product strength or expressing the strength in a manner that is incongruent with the dosage and administration of the product complicates the calculating of dosage and may lead to dosing errors. We recommend expressing the recommended dosage in "mg/kg" to ensure the unit of measure for the strength (mg) and dose (mg/kg) in the Prescribing Information are consistent.

d. The preparation and administration instructions are complex; therefore we recommend including the statement, "See Full Prescribing Information for instructions on preparation and administration. (2.4)".

3. Dosage Forms and Strengths Section
a. Numeric doses and strength are presented in multiple units of measure. For example, the recommended dosage is presented in units of "\frac{mg}{kg}" and the strength is presented in units of "mg". Developing a product strength or expressing the strength in a manner that is incongruent with the dosage and administration of the product complicates the calculating of dosage and may lead to dosing errors. We recommend expressing the strength in "mg/kg" to ensure the unit of measure for the strength and dose in the Prescribing Information are consistent.

b. The dosage form lacks clarity and missing the placeholder, "-xxxx" for the nonproprietary name. Therefore, we recommend revising the following statement, to "For injection: 10 mg of loncastuximab tesirine -xxxx as a lyophilized powder in a single-dose vial for reconstitution and dilution. (3)"

B. Prescribing Information

1. Dosage and Administration Section
a. Section 2.1 Recommended Dosage
i. The frequency of administration is expressed with the abbreviation, "Q3W". Certain abbreviations should not be used in the Prescribing Information because they are frequently misinterpreted and can lead to medication errors that may result
in patient harm. We recommend replacing the abbreviation, “Q3W” with the intended meaning, “every 3 weeks”.

b. Section 2.2 Recommended Premedication

i. The frequency of administration is expressed with the abbreviation, “BID”. Certain abbreviations should not be used in the Prescribing Information because they are frequently misinterpreted and can lead to medication errors that may result in patient harm. We recommend replacing the abbreviation, “BID” with the intended meaning, “twice daily”.

c. Section 2.3 Dose Delays and Modifications

i. As currently presented, the dose delays and modifications contains the symbol, “≥”. Error prone symbols may lead to misinterpretation and medication error. We recommend replacing the symbol, “≥” with the intended meaning.

d. Section 2.4 Reconstitution and Administration Instructions

i. We recommend revising the dose calculation section by presenting the dose as and deleting the calculation equation as this statement is not needed.

ii. We recommend revising the concentration after reconstitution to be expressed in as the strength will be presented as .

iii. The reconstitution instructions lack clarity, which may lead to product preparation errors. Therefore we recommend:

   a. For the first bullet, clarify if the dose is calculated using the patient’s actual weight or ideal body weight.

   b. We note there is equation included to calculate the dose . Developing a product strength or expressing the strength in a manner that is incongruent with the dosage and administration of the product complicates the calculating of dosage and may lead to dosing errors. We recommend ensuring the unit of measure for the strength and dose in the Prescribing Information are consistent.
c. Revise the statement, to “Reconstitute each vial with 2.2 mL of Sterile Water for Injection, USP, with the stream directed toward the inside wall of the vial to obtain a final concentration of XX/mL.” for clarity and to use present tense.

d. Revise the statements, to “Use reconstituted 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 at room temperature 20°C to 25°C (68°F to 77°F).” for clarity and to use present tense.

iv. The dilution instructions lack clarity, which may lead to product preparation errors. Therefore we recommend:

a. Add as the first bullet the statement to “Determine the volume of XX/mL reconstituted solution needed based on the required dose.”.

b. Revise the bullet to read “Add the calculated dose volume of solution into a 50 mL infusion bag of 5% Dextrose Injection, USP.” We also recommend deleting

c. In the third bullet, revise the statement to “If not used immediately, store the diluted infusion solution refrigerated”.
v. The administration instructions lack clarity, which may lead to product administration errors. Therefore we recommend:

   a. Merge the first two bullets to “Administer by intravenous infusion over 30 minutes using a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2- or 0.22-micron pore size) and catheter.”.

2. Dosage Forms and Strengths

   a. The dosage form is missing the placeholder, “-xxxx” for the nonproprietary name. Therefore, we recommend revising the following statement, to “For injection: 10 mg of loncastuximab tesirine-xxxx as a lyophilized powder in a single-dose vial for reconstitution and further dilution.”

   b. Numeric doses and strength are presented in multiple units of measure. For example, the recommended dosage is presented in units of,” and the strength is presented in units of “mg”. Developing a product strength or expressing the strength in a manner that is incongruent with the dosage and administration of the product complicates the calculating of dosage and may lead to dosing errors. We recommend expressing the strength in to ensure the unit of measure for the strength and dose in the Prescribing Information are consistent.

C. Patient Information

1. In the title, we recommend including the correct dosage form, “for injection”. Therefore, revise the statement, to “(loncastuximab tesirine-xxxx) for injection, for intravenous use”.

2. In the section, “What are the ingredients in “-xxxx”?, the active ingredient, Loncastuximab tesirine is missing the placeholder, “-xxxx” for the nonproprietary name. Therefore, we recommend revising the nonproprietary from to “Loncastuximab tesirine-xxxx”.

Reference ID: 4753525
4.2 RECOMMENDATIONS FOR ADC THERAPEUTICS SA

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. Numeric doses and strength are presented in multiple units of measure. For example, the recommended dosage is presented in units of "and" and the strength is presented in units of "mg". Developing a product strength or expressing the strength in a manner that is incongruent with the dosage and administration of the product complicates the calculating of dosage and may lead to dosing errors. We recommend expressing the strength in "mg" to ensure the unit of measure for the strength and dose in the Prescribing Information are consistent.

2. 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.

3. 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.

B. Container Label

1. 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.

2. Loncastuximab tesirine-xxxx is hazardous; however the principal display panel of the container label does not convey this information. Hazardous products
require special handling procedures. If space is permitting, consider adding the statement, “CAUTION: Hazardous Agent” in bold red font on the principal display panel of the container label or on the side panel.

C. Carton Labeling

1. Revise the “Reconstitute and dilute prior to administration” statement to clearly state that product must be reconstituted with Sterile Water for Injection, USP and diluted with 5% Dextrose Injection, USP to prevent any preparation errors. Revise to “Reconstitution: Reconstitute with 2.2 mL Sterile Water for Injection, USP.” and “Dilution: Must be further diluted with 5% Dextrose Injection, USP.”.

2. 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, “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.”

3. We recommend revising the word, [removed] to “hazardous” on the carton labeling to reflect alignment with current terminology recommended in labeling for hazardous drug. Revise [removed] to “CAUTION: Hazardous Agent” in bold red font.

4. To ensure consistency with the terminology in the Prescribing Information, we recommend revising the recommended dosage statement to read, “Dosage: See Prescribing Information.”

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Loncastuximab tesirine-xxxx received on September 21, 2020 from ADC Therapeutics SA.

<table>
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<th>Table 2. Relevant Product Information for Loncastuximab tesirine-xxxx</th>
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<td><strong>Dosage Form</strong></td>
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<tr>
<td>Strength</td>
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| **Dose and Frequency** | Loncastuximab tesirine-xxxx as an intravenous infusion is administered over 30 minutes on Day 1 of each cycle (every 3 weeks). Administer intravenous infusion as follows:  
  - 150 mcg/kg every 3 weeks for 2 cycles  
  - 75 mcg/kg every 3 weeks for subsequent cycles |
| **How Supplied** | Loncastuximab tesirine-xxxx is a preservative-free, white to off-white lyophilized powder, which has a cake-like appearance, supplied in a single-dose vial. Each carton contains one 10 mg single-dose vial. |
| **Storage**    | Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not use beyond the expiration date shown on the carton. Do not freeze. Do not shake. |
APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 1, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, loncastuximab tesirine. Our search did not identify any previous label and labeling reviews.
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following loncastuximab tesirine-xxx labels and labeling submitted by ADC Therapeutics SA.

- Container label received on September 21, 2020
- Carton labeling received on September 21, 2020
- Prescribing Information and Patient Information (Image not shown) received on September 21, 2020, available from \CDSESUB1\evsprod\bla761196\0002\m1\us\draft-labeling-text.pdf

G.2 Label and Labeling Images

Container label

---

\[\text{Reference ID: 4753525}\]

---

Carton labeling
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/
HINA S MEHTA on behalf of NICOLE F IVERSON
02/26/2021 10:46:54 AM

HINA S MEHTA
02/26/2021 10:47:57 AM
Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

<table>
<thead>
<tr>
<th>Submission</th>
<th>BLA 761196</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submission Number</td>
<td>0002</td>
</tr>
<tr>
<td>Submission Date</td>
<td>9/21/2020</td>
</tr>
<tr>
<td>Date Consult Received</td>
<td>10/5/2020</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Loncastuximab tesirine (ADCT-402)</td>
</tr>
<tr>
<td>Indication</td>
<td>Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after at least two prior systemic therapies.</td>
</tr>
<tr>
<td>Therapeutic dose</td>
<td>150 mcg/kg every 3 weeks (Q3W) for 2 cycles followed by 75 mcg/kg Q3W for subsequent cycles.</td>
</tr>
<tr>
<td>Clinical Division</td>
<td>DHM2</td>
</tr>
</tbody>
</table>

Note: Any text in the review with a light background should be inferred as copied from the sponsor’s document.

This review responds to your consult dated 10/5/2020 regarding the sponsor’s QT evaluation. We reviewed the following materials:

- Previous IRT review under IND 126138 dated 03/09/2018 in DARRTS;
- Summary of clinical pharmacology (Submission 0002; link);
- Toxicology written summary (Submission 0002; link);
- Sponsor’s cardiac safety report for study ADCT-402-201 (Submission 0002; link);
- Sponsor’s clinical study report for the study (Submission 0002; link); and
- Sponsor’s draft proposed labeling (Submission 0002; link).

1 SUMMARY

No large mean increases in the QTc interval (i.e., >20 msec) were observed in this QT assessment of loncastuximab tesirine (ADCT-402).

The effect of loncastuximab tesirine was evaluated in a single-arm, Phase 2, open-label, study in patients with relapsed or refractory diffuse large B-Cell lymphoma (DLBCL) (Study ADCT-402-201). The highest dose tested was the therapeutic dose. The data were analyzed using the by-timepoint analysis as the primary analysis, which suggested that loncastuximab tesirine is not associated with large mean increases on the QTc interval – see Table 1 for the overall results for the first two cycles. The findings of this analysis are further supported by the available nonclinical data (section 3.1.2) and categorical analysis (section 4.4).
Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

<table>
<thead>
<tr>
<th>ECG parameter</th>
<th>Treatment</th>
<th>Time</th>
<th>ΔQTcF</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc</td>
<td>150 ug/kg Q3W x2 cycles</td>
<td>Cycle 2 Day 1 End-of-Infusion</td>
<td>8.4</td>
<td>(6.1, 10.7)</td>
</tr>
</tbody>
</table>

For further details on the FDA analysis, please see section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR
Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION
Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES
Not applicable.

2.2 PROPOSED LABEL
Below are proposed edits to the label submitted to Submission 0002 (link) from the IRT. Our changes are highlighted (addition, deletion) for suggestions only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At the maximum recommended therapeutic dose of /kg during Cycle 1 and Cycle 2, loncastuximab tesirine does not cause large mean increases (i.e. >20 msec) in the QTc interval.

Reviewer’s comment:

- We propose to state the target effect size for the QT assessment.

- We agree with the sponsor’s conclusion (i.e. a lack of large mean effect), however, we do not agree with the sponsor’s selection of primary analysis method and the reporting of analysis results. We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.
3 SPONSOR’S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Loncastuximab tesirine is under clinical development for the treatment of adult patients with relapsed or refractory DLBCL including high grade B-cell lymphoma, after at least two prior systemic therapies. It is a CD19-targeted antibody-drug conjugate (ADC), consisting of a humanized IgG1 kappa monoclonal antibody (mAb) specific for binding to human CD19, conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxic drug, through a protease-cleavable valine-alanine linker. The attachment of SG3199 to the valine-alanine linker is known as tesirine. Once bound to CD19, loncastuximab tesirine is internalized and the cleavable valine-alanine linker is cleaved by lysosomal proteases releasing free dimers (SG3199) inside the target cell. The dimers are highly effective anticancer drugs that covalently bind in the minor groove of the DNA and form highly cytotoxic DNA interstrand cross-links which subsequently cause the arrest of the cell and its death.

Loncastuximab tesirine for injection is supplied as a sterile, whitish, preservative-free, lyophilized powder for intravenous infusion after reconstitution and dilution. It is administered as an intravenous infusion over 30 minutes Q3W with the therapeutic dose of 150 mcg/kg Q3W for 2 cycles followed by 75 mcg/kg Q3W for subsequent cycles.

Previously, the IRT reviewed the QT study protocol ADCT-402-201 and agreed with the sponsor’s plan to exclude large mean effects (i.e., > 20 msec) for the oncology indication. Further, it was communicated that the by-timepoint analysis should be used as the primary analysis and that exposure-response (concentration-QTc) analysis should be carried out as a supportive secondary analysis for the small molecule component of ADC, i.e., SG3199 (refer to IRT review in DARRTS dated 3/9/2018).

ADCT-402-201 is a single-arm Phase 2, open-label, study in patients with relapsed or refractory DLBCL. The drug was administered as an IV infusion over 30 minutes on Day 1 of each cycle, and 145 patients received 150 μg/kg Q3W for 2 cycles, then 75 μg/kg Q3W for subsequent cycles. There are no major changes in dosing regimen, PK/ECG schedule, and analysis methods after the previous IRT review.

Highlights of Clinical Pharmacology:

The geometric mean concentration of loncastuximab tesirine conjugated antibody at the end of infusion of cycle 2 was 2734 ng/mL (CV=35.8%). The geometric mean AUC was 26,902 ng∙day/mL (CV%=33.4). Cycle 2 provides for the highest exposure of the intravenous infusion at the therapeutic dose. The half-life of conjugated antibody for patients was 14.6 days at Cycle 1 and 20.6 days at steady state. Following two cycles of treatment, a 1.65-times accumulation of the conjugated antibody was observed. Age, sex, race, body weight showed no effect. Pharmacokinetics were comparable between mild and moderate renally impaired patients and those with normal renal function. Similarly, mild hepatically impaired patients had pharmacokinetics comparable to those with normal hepatic function. Cytochrome P450s are not involved.
The majority of PK samples for SG3199 were below the LLOQ (0.025 ng/mL). In the limited SG3199 evaluable patients, the maximum concentration are reported between 0.05-0.1 ng/mL in different studies.

### 3.1.2 Nonclinical Safety Pharmacology Assessments

In intravenous infusion repeated dose toxicity studies in the cynomolgus monkey, the sponsor concluded that the administration of ADCT-402 was not associated with any mortalities or changes in food consumption, cardiovascular parameters (as assessed by electrocardiogram [ECG] and blood pressure), urinalysis or ophthalmic examinations.

There is no mention of in vitro hERG study for SG3199 or tesirine in the submission.

### 3.2 Sponsor’s Results

#### 3.2.1 By-Time Analysis

Loncastuximab tesirine (ADCT-402) excluded the 20 msec threshold at the therapeutic dose level for ΔQTcF in the sponsor’s by-time point analysis.

The sponsor used exposure-response analysis as the primary analysis for ADCT-402 even when we commented that by-time point analysis should be used as primary analysis. Please see section 3.2.3 for additional details.

**Reviewer’s comment:** The reviewer’s independent by-time point analysis drew consistent conclusion with that of the sponsor’s analysis, i.e., exclusion of 20 msec in ΔQTcF at therapeutic dose level of the research product.

#### 3.2.1.1 Assay Sensitivity

Not applicable.

#### 3.2.1.1.1 QT Bias Assessment

Not applicable.

#### 3.2.2 Categorical Analysis

The sponsor listed outlier analysis for ΔQTcF (i.e., >30 but ≤60 msec or >60 msec over baseline). ΔQTcF>60 msec was found in one patient (0.7%). For HR, PR and QRS, the sponsor claimed there was no consistent or meaningful change from baseline values to posttreatment values.

**Reviewer’s comment:** The reviewer’s independent categorial analyses showed consistent results in ΔQTcF outliers. Please see section 4.4 for the reviewer’s detailed analyses in QTcF, HR, PR and QRS outliers.

#### 3.2.3 Exposure-Response Analysis

The sponsor evaluated the relationship between conjugated antibody serum concentrations and ΔQTcF using a linear mixed-effects modeling approach with ΔQTcF as the dependent variable and the serum concentration of the conjugated antibody as the independent variable. The model included serum concentration, time, treatment, intercept and subject were included as random effects. The estimated population slope of
the conjugated antibody concentration-QTc relationship was 0.002 msec per ng/mL (90% CI: 0.0014 to 0.0028), with an intercept of -0.6 msec (90% CI: -2.43 to 1.22). The sponsor concluded that in order to reach the threshold of 20 msec the value of Cmax would need to be 7,820 ng/ml.

According to the sponsor, around 98% of the SG3199 concentrations were below the quantification limit, and therefore, the relationship between QTcF and SG3199 concentration was difficult to evaluate.

**Reviewer’s comments:** The reviewer did not conduct independent concentration-QTc analysis for the following reasons:

1) Because mAb and the ADC have a low likelihood of direct ion channel interactions, an exposure-response analysis with ADC or mAb as the concentration covariate is not meaningful.

2) Only 25 ECG-PK pairs from 15 unique subjects cross treatment cycles 1-13 were available for the exposure-response analysis using SG3199 as the concentration covariate. The reviewer agreed with the sponsor that the data are not sufficient for a reliable model.

3) The maximum concentration for SG3199 is below the nanomolar scale. In the 25 PK/ECG pairs, the average SG3199 concentration is 50.9 pg/mL (range: 25.1-144 pg/mL).

### 3.2.4 Safety Analysis

Of the 145 patients in the All-Treated Population, 143 patients (98.6%) had at least one TEAE; 117 patients (80.7%) had at least one TEAE related to loncastuximab tesirine; and 105 patients (72.4%) had at least one TEAE of Grade ≥3. Fifty-seven patients (39.3%) had at least one serious TEAE; 8 patients (5.5%) had a TEAE leading to a fatal outcome; and 34 patients (23.4%) had a TEAE leading to withdrawal of treatment. Seven patients (4.8%) had an infusion-related reaction.

TEAE listed under the SOC Cardiac disorders occurred in 19 (13.1%) patients. Cardiac-related TEAEs reported in more than 2 patients were tachycardia (11, 7.6%), pericardial effusion (4, 2.8%), angina pectoris (2, 1.4%) and acute myocardial infarction (2, 1.4%). Two cardiac TEAEs were considered serious (pericardial effusion and pericarditis) and none had a fatal outcome.

There were 5 patients (3.4%) who experienced a TEAE of ECG QT prolonged. Of these 5 patients, one patient experienced ECG QT prolonged (2 events) and ECG-T-wave inversion. In addition, one patient each experienced acute myocardial infarction, atrioventricular block, supraventricular tachycardia, and ventricular extrasystoles. There was one additional patient (0.7%) with syncope.

For heart rate, PR interval and QRS duration, there was no consistent or meaningful change from baseline values to posttreatment values during cycles. One patient (0.7%) had QTcF increase from baseline of >60 msec.
4 REVIEWERS’ ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD
The sponsor used QTcF for the primary analysis. This is acceptable as no large increases or decreases in heart rate (i.e. \(|\text{mean}| < 10 \text{ beats/min}\)) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall
Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment
Not applicable.

4.3 BY-TIME ANALYSIS
The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG.

At each time point, the statistical reviewer used linear mixed model (ANCOVA) to analyze the drug effect for each biomarker (e.g., ΔQTcF, ΔHR) independently. The model includes treatment as a fixed effect and baseline as a covariate.

4.3.1 QTc
Figure 1 displays the time profile of ΔQTcF for loncastuximab tesirine treatment. The ΔQTcF values are shown in Table 2.
Figure 1: Mean and 90% CI of ΔQTcF Time Course (unadjusted CIs).

Table 2: The Point Estimates and the 90% CIs for ΔQTcF

<table>
<thead>
<tr>
<th>Cycle/Day/Time</th>
<th>N</th>
<th>LSMean</th>
<th>SE</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C01D01 EOI</td>
<td>144</td>
<td>3.3</td>
<td>0.8</td>
<td>(2.0, 4.6)</td>
</tr>
<tr>
<td>C01D01 Post 4h</td>
<td>138</td>
<td>3.5</td>
<td>0.8</td>
<td>(2.1, 4.8)</td>
</tr>
<tr>
<td>C01D08 Post 168h</td>
<td>139</td>
<td>-6.6</td>
<td>1.2</td>
<td>(-8.6, -4.6)</td>
</tr>
<tr>
<td>C01D15 Post 336h</td>
<td>131</td>
<td>-4.8</td>
<td>1.3</td>
<td>(-6.9, -2.6)</td>
</tr>
<tr>
<td>C02D01 BeforeDose</td>
<td>120</td>
<td>6.9</td>
<td>1.2</td>
<td>(4.9, 8.9)</td>
</tr>
<tr>
<td>C02D01 EOI</td>
<td>120</td>
<td>8.4</td>
<td>1.4</td>
<td>(6.1, 10.7)</td>
</tr>
<tr>
<td>C02D01 Post 4h</td>
<td>110</td>
<td>7.1</td>
<td>1.4</td>
<td>(4.8, 9.3)</td>
</tr>
<tr>
<td>C02D08 Post 168h</td>
<td>113</td>
<td>-4.9</td>
<td>1.4</td>
<td>(-7.2, -2.6)</td>
</tr>
<tr>
<td>C02D15 Post 336h</td>
<td>113</td>
<td>-0.7</td>
<td>1.6</td>
<td>(-3.3, 1.9)</td>
</tr>
<tr>
<td>C03D01 BeforeDose</td>
<td>85</td>
<td>7.2</td>
<td>1.7</td>
<td>(4.4, 10.0)</td>
</tr>
<tr>
<td>C03D01 EOI</td>
<td>84</td>
<td>9.4</td>
<td>1.7</td>
<td>(6.5, 12.2)</td>
</tr>
<tr>
<td>C05D01 BeforeDose</td>
<td>47</td>
<td>7.3</td>
<td>2.0</td>
<td>(3.9, 10.7)</td>
</tr>
<tr>
<td>Cycle/Day/Time</td>
<td>N</td>
<td>LSMean</td>
<td>SE</td>
<td>90% CI</td>
</tr>
<tr>
<td>----------------------</td>
<td>----</td>
<td>--------</td>
<td>-----</td>
<td>--------------</td>
</tr>
<tr>
<td>C07D01 BeforeDose</td>
<td>27</td>
<td>6.2</td>
<td>2.5</td>
<td>(2.0, 10.4)</td>
</tr>
<tr>
<td>C09D01 BeforeDose</td>
<td>20</td>
<td>6.9</td>
<td>2.6</td>
<td>(2.5, 11.4)</td>
</tr>
<tr>
<td>C11D01 BeforeDose</td>
<td>11</td>
<td>1.5</td>
<td>2.2</td>
<td>(-2.5, 5.5)</td>
</tr>
<tr>
<td>C13D01 BeforeDose</td>
<td>6</td>
<td>13.5</td>
<td>2.6</td>
<td>(8.0, 19.0)</td>
</tr>
<tr>
<td>C15D01 BeforeDose</td>
<td>1</td>
<td>-4.3</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

### 4.3.1.1 Assay sensitivity

Not applicable.

### 4.3.2 HR

Figure 2 displays the time profile of ΔHR for loncastuximab tesirine treatment.
4.3.3 ΔPR

Figure 3 displays the time profile of ΔPR for loncastuximab tesirine treatment.
4.3.4 ΔQRS

Figure 4 displays the time profile of ΔQRS for loncastuximab tesirine treatment.
4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

Table 3 lists the number of subjects as well as the number of observations whose QTcF values were ≤450 msec, between 450 and 480 msec, between 480 and 500 msec and greater than 500 msec.
Table 3: Categorical Analysis for QTcF (maximum)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total N</th>
<th>QTcF&lt;=450 msec</th>
<th>450&lt;QTcF&lt;=480 msec</th>
<th>480&lt;QTcF &lt;=500 msec</th>
<th>QTcF&gt;500 msec</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subj. #</td>
<td>Obs. #</td>
<td>Subj. #</td>
<td>Obs. #</td>
<td>Subj. #</td>
</tr>
<tr>
<td>Baseline</td>
<td>144</td>
<td>144</td>
<td>134 (93.1%)</td>
<td>134 (93.1%)</td>
<td>9 (6.3%)</td>
</tr>
<tr>
<td>Loncastuximab Tesirine 150 ug/kg</td>
<td>144</td>
<td>1506</td>
<td>109 (75.7%)</td>
<td>1351 (89.7%)</td>
<td>27 (18.8%)</td>
</tr>
</tbody>
</table>

Table 4 lists the categorical analysis results for ΔQTcF (less than 30 msec, between 30 and 60 and greater than 60 msec).

Table 4: Categorical Analysis for ΔQTcF (maximum)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total N</th>
<th>ΔQTcF&lt;=30 msec</th>
<th>30&lt;ΔQTcF&lt;=60 msec</th>
<th>ΔQTcF&gt;60 msec</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subj. #</td>
<td>Obs. #</td>
<td>Subj. #</td>
<td>Obs. #</td>
</tr>
<tr>
<td>Loncastuximab Tesirine 150 ug/kg</td>
<td>144</td>
<td>1506</td>
<td>120 (83.3%)</td>
<td>1447 (96.1%)</td>
</tr>
</tbody>
</table>

4.4.2 HR

Table 5 lists the categorical analysis results for maximum HR (<=100 beats/min and >100 beats/min) and Table 6 lists the categorical analysis results for minimum HR (>45 beats/min and <=45 beats/min).

Table 5: Categorical Analysis for HR (maximum)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total N</th>
<th>HR&lt;=100 beats/min</th>
<th>HR&gt;100 beats/min</th>
<th>HR&gt;100 beats/min &amp; Increase &gt;25%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subj. #</td>
<td>Obs. #</td>
<td>Subj. #</td>
<td>Obs. #</td>
</tr>
<tr>
<td>Baseline</td>
<td>144</td>
<td>144</td>
<td>133 (92.4%)</td>
<td>133 (92.4%)</td>
</tr>
<tr>
<td>Loncastuximab Tesirine 150 ug/kg</td>
<td>144</td>
<td>1506</td>
<td>98 (68.1%)</td>
<td>1400 (93.0%)</td>
</tr>
</tbody>
</table>

Table 6: Categorical analysis for HR (minimum)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total N</th>
<th>HR&gt;45 beats/min</th>
<th>HR&lt;=45 beats/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subj. #</td>
<td>Obs. #</td>
<td>Subj. #</td>
</tr>
<tr>
<td>Baseline</td>
<td>144</td>
<td>144</td>
<td>144 (100%)</td>
</tr>
<tr>
<td>Loncastuximab Tesirine 150 ug/kg</td>
<td>144</td>
<td>1506</td>
<td>143 (99.3%)</td>
</tr>
</tbody>
</table>

4.4.3 PR

Table 7 lists the categorical analysis results for PR (less than 220 msec; greater than 220 msec and above 220 msec with 25% increase over baseline).
Table 7: Categorical Analysis for PR

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total N</th>
<th>PR≤=220 msec</th>
<th>PR&gt;220 msec</th>
<th>PR&gt;220 msec &amp; Increase &gt;25%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subj. #</td>
<td>Obs. #</td>
<td>Subj. #</td>
<td>Obs. #</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>139</td>
<td>139</td>
<td>134 (96.4%)</td>
<td>134 (96.4%)</td>
</tr>
<tr>
<td>Loncastuximab Tesirine 150 ug/kg</td>
<td>139</td>
<td>1445</td>
<td>132 (95.0%)</td>
<td>1425 (98.6%)</td>
</tr>
</tbody>
</table>

4.4.4 QRS

Table 8 lists the categorical analysis results for QRS (less than 120 msec, greater than 120 msec and above 120 msec with 25% increase over baseline).

Table 8: Categorical Analysis for QRS

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total N</th>
<th>QRS≤=120 msec</th>
<th>QRS&gt;120 msec</th>
<th>QRS&gt;120 msec &amp; Increase &gt;25%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subj. #</td>
<td>Obs. #</td>
<td>Subj. #</td>
<td>Obs. #</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>144</td>
<td>144</td>
<td>127 (88.2%)</td>
<td>127 (88.2%)</td>
</tr>
<tr>
<td>Loncastuximab Tesirine 150 ug/kg</td>
<td>144</td>
<td>1506</td>
<td>121 (84.0%)</td>
<td>1303 (86.5%)</td>
</tr>
</tbody>
</table>

4.5 EXPOSURE-RESPONSE ANALYSIS

The reviewer did not conduct independent exposure-response analysis. Refer to reviewer’s comments in section 3.2.3 of this review.

4.5.1.1 Assay sensitivity

Not applicable.
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/

NAN ZHENG
11/30/2020 12:59:36 PM
Raman Baweja is the primary clinical pharmacology reviewer.

RAMAN K BAWEJA
11/30/2020 01:15:19 PM

JANELL E CHEN
11/30/2020 01:16:29 PM

DALONG HUANG
11/30/2020 01:18:01 PM

CHRISTINE E GARNETT
11/30/2020 01:24:10 PM