BLA 761196

BLA ACCELERATED APPROVAL

ADC Therapeutics SA
c/o ADC Therapeutics America Inc.
Attention: Rupal Patel
Associate Director, Global Regulatory Affairs
430 Mountain Avenue, Suite 404 (4th Floor)
Murray Hill, NJ 07974

Dear Ms. Patel:

Please refer to your biologics license application (BLA) dated September 21, 2020, received September 21, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Zynlonta (loncastuximab tesirine-lpyl) for injection.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2166 to ADC Therapeutics SA, Epalinges, Switzerland, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Zynlonta (loncastuximab tesirine-lpyl). Zynlonta is indicated for the 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.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture loncastuximab monoclonal antibody intermediate [redacted (b) (4)], and SG3249 drug linker intermediate [redacted (b) (4)]. You are approved to manufacture loncastuximab tesirine-lpyl drug substance and drug product at [redacted (b) (4)]. The final formulated product will be labeled and packaged at [redacted (b) (4)]. You may label your product with the proprietary name Zynlonta and will market it as 10 mg for injection, as a lyophilized powder in a single-dose vial.

DATING PERIOD

The dating period for Zynlonta shall be 24 months from the date of manufacture when stored at 5 ± 3°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at ≤ (b) (4). The dating period for your monoclonal antibody intermediate shall be (b) (4) months from the date of manufacture when stored at ≤ (b) (4). The dating period for your drug linker intermediate shall be (b) (4) months from the date of manufacture when stored at ≤ (b) (4). We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your monoclonal antibody intermediate, drug linker intermediate, drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Zynlonta to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Zynlonta, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 601.41), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the Food and Drug Administration (FDA) automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL)

format, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted on March 12, 2021, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761196**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for loncastuximab tesirine-lpyl was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated April 16, 2021. This requirement, along with required completion dates, is listed below.

4029-1 Conduct a randomized, phase 3 clinical trial to verify and describe the clinical benefit of loncastuximab tesirine-lpyl in patients with relapsed or refractory large B-cell lymphoma. The trial should include sufficient numbers of racial and ethnic minority patients to better reflect the U.S. patient population and allow for interpretation of the results in these patient populations. Patients should be randomized to receive

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

loncastuximab tesirine-lpyl plus immunotherapy or immunochemotherapy. The primary endpoint should be progression-free survival, with secondary endpoints that include overall survival and objective response rate.

Final Protocol Submission:	03/2020
Trial Completion:	06/2025
Final Report Submission:	12/2025

Submit clinical protocols to your IND 126138 for this product. In addition, under 21 CFR 601.70 you should include a status summary of each requirement in your annual report to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 12 months because the necessary studies are impossible or highly impracticable. This is because the incidence of non-Hodgkin lymphoma in patients 0 to 12 months of age is extremely rare.

We are deferring submission of your pediatric study for ages 1 to 17 years for this application because pediatric studies should be delayed until additional safety or effectiveness data for loncastuximab tesirine-lpyl have been collected to inform a pediatric study.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

4029-2 Conduct a study assessing the efficacy and safety of loncastuximab tesirine-lpyl in pediatric patients 1 year or older with relapsed or refractory non-Hodgkin lymphoma. The safety endpoints should determine safety and tolerability of loncastuximab tesirine-lpyl and identify the

recommended dose and schedule. The efficacy endpoints should determine activity as assessed by response rate and durability of response.

Final Protocol Submission:	07/2022
Study Completion:	07/2027
Final Report Submission:	07/2028

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 126138, with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risk of edema, effusion, cutaneous reactions and inflammatory-related conditions associated with the administration of loncastuximab tesirine-lpyl.

Additionally, 505(k)(1) of the FDCA will not be sufficient to assess the known risks of serious adverse events and severe neutropenia when loncastuximab tesirine-lpyl is administered in combination with immunochemotherapy among U.S. racial and ethnic minority patients with large B-cell lymphoma.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

[3] See the draft guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

4029-3 Conduct a comprehensive analysis evaluating and characterizing the incidence, clinical presentation, management, and outcomes of the potential serious risks of loncastuximab tesirine-associated toxicities of edema, effusion, cutaneous reactions, and inflammatory-related conditions. Submit an integrated final report from patient-level and pooled analyses of ongoing and completed clinical trials, postmarketing reports and/or literature reports and a comprehensive pharmacovigilance assessment for these potential serious risks.

The timetable you submitted on April 16, 2021, states that you will conduct this study according to the following schedule:

Draft Analysis Plan Submission:	12/2021
Final Analysis Plan Submission:	06/2022
Study Completion:	09/2025
Final Report Submission:	03/2026

4029-4 Submit an integrated final report containing data from clinical trials to further characterize the exposure of loncastuximab tesirine-lpyl monotherapy and in combination with immunochemotherapy, the increased risk of severe and serious adverse events, including severe neutropenia, and efficacy among U.S. racial and ethnic minority patients with large B-cell lymphoma. Provide the population pharmacokinetic and exposure-response analyses for both efficacy and safety in the interim report.

The timetable you submitted on April 16, 2021, states that you will conduct this study according to the following schedule:

Draft Analysis Plan Submission:	12/2021
Final Analysis Plan Submission:	06/2022
Interim Report Submission:	03/2025
Study Completion:	09/2025
Final Report Submission:	03/2026

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of higher drug exposure when loncastuximab tesirine-lpyl is administered in patients with moderate and severe hepatic impairment.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

4029-5 Conduct an open-label, non-randomized, dose-escalation trial to determine a safe and appropriate dosing regimen of loncastuximab tesirine-lpyl in patients with moderate and severe hepatic impairment,

according to the National Cancer Institute Organ Dysfunction Working Group criteria in the target patient population. Collect safety and pharmacokinetic information for loncastuximab tesirine-lpyl and SG3199 to determine the appropriate starting dose and dosing regimen of loncastuximab tesirine-lpyl for this population.

The timetable you submitted on April 16, 2021, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	12/2021
Final Protocol Submission:	09/2022
Trial Completion:	12/2026
Final Report Submission:	06/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 126138 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

[4] See the draft guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4029-6 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-lpyl 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-lpyl. The final report should include nAb assay validation report and assay standard operating procedure.

The timetable you submitted on April 16, 2021 states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2022

4029-7 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.

The timetable you submitted on April 16, 2021 states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2022

Submit clinical protocols to your IND 126138 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Jennifer Lee, Senior Regulatory Health Project Manager, at (240) 402-4622.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container 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/

MARC R THEORET
04/23/2021 11:27:38 AM