IND 126138

MEETING MINUTES

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:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ADCT-402.

We also refer to the teleconference between representatives of your firm and the FDA on April 17, 2020. The purpose of the meeting was to discuss the content and presentation of data to be included in your planned BLA submission.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

Nicholas Richardson, DO, MPH
Acting Clinical Team Leader
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] 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.

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: Friday, April 17, 2020; 9:00 AM – 10:00 AM (ET)
Meeting Location: Teleconference

Application Number: IND 126138
Product Name: ADCT-402
Proposed Indication: Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)
Sponsor Name: ADC Therapeutics SA
Regulatory Pathway: 505(b)(1) of the Food, Drug, and Cosmetics Act and 351(a) of the Public Health Service Act

Meeting Chair: Nicholas Richardson, DO, MPH
Meeting Recorder: Jennifer Lee, PharmD, RAC-US

FDA ATTENDEES

Office of Oncologic Diseases (OOD)
Elizabeth Everhart, MSN, RN, ACNP – Acting Program Manager for Safety

OOD/Division of Hematologic Malignancies II
Nicole Gormley, MD – Acting Director
Nicholas Richardson, DO, MPH – Acting Clinical Team Leader
Maryam Yazdy, MD – Clinical Reviewer

Office of Regulatory Operations/Division of Regulatory Operations for Oncologic Diseases
Theresa Carioti, MPH – Chief, Project Management Staff
Jennifer Lee, PharmD, RAC-US – Senior Regulatory Health Project Manager

Office of Hematology and Oncology Products/Division of Hematology, Oncology, Toxicology
Haleh Saber, PhD – Deputy Director
Brenda Gehrke, PhD – Acting Team Leader
Natalie Simpson, PhD – Pharmacologist

Office of Biostatistics/Division of Biometrics IX
Yu-te Wu, PhD – Biometrics Team Leader
Qing Xu, PhD – Biometrics Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Ruby Leong, PharmD, BCOP – Clinical Pharmacology Team Leader
Hisham Qosa, PhD – Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of Biotechnology Products/Division Of Biotechnology Review and Research IV
Haoheng Yan, MD, PhD – Lead Chemist
Rukman De Silva, PhD – Chemist

OPQ/Office of Pharmaceutical Manufacturing Assessment/Division of Biotechnology Manufacturing, Branch I
Dupeh Palmer-Ochieng, PhD – Microbiologist

OPQ/Office of New Drug Products/Division of New Drug API
Sherita McLamore, PhD – Chemist
Rohit Tiwari, PhD – Chemist

SPONSOR ATTENDEES

Jay Feingold MD, PhD, Senior Vice President and Chief Medical Officer, ADCT
Jens Wuerthner MD, PhD, Vice President, Head of Global Clinical Development Oncology, Clinical, ADCT
David Ungar MD, Head of US Oncology Clinical Development, ADCT
Joe Boni PhD, Head of Global Clinical Pharmacology, ADCT
David Ellis PhD, Vice President, Regulatory Affairs, ADCT
Rupal Patel, Associate Director, Regulatory Affairs, ADCT
Shui He PhD, Vice President, Global Biometrics, ADCT
Karthik Mani, Associate Director, CMC Regulatory Affairs, ADCT
(b) (4)
Karin Havenith, Principal BioAnalytical Scientist, R&D, ADCT
Esohe Idusogie PhD, Head of Process Quality and CMC Analytical, ADCT
Michael Mulkerrin, PhD, Vice President, Head of CMC, ADCT

1.0 BACKGROUND

Loncastuximab tesirine (ADCT-402) is an antibody drug conjugate composed of a proposed CD19 targeting humanized monoclonal immunoglobulin (IgG1) conjugated via a linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin, currently under development by ADC Therapeutics SA for the treatment of CD19-positive B cell hematologic malignancies.

The Sponsor is currently targeting a 3rd quarter 2020 submission of an original Biologics License Application (BLA) to propose the registration of ADCT-402 for the treatment of patients with relapsed or refractory DLBCL. Results from the ongoing Phase 2 Study

ADCT-402-201, entitled "*A Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)),"* will provide the basis for the planned application.

On February 4, 2020, the Sponsor requested a Pre-BLA meeting with the Agency to discuss the content and presentation of data to be included in the planned BLA. A revised list of meeting questions was received on February 7, 2020.

FDA sent Preliminary Comments to ADC Therapeutics SA on April 9, 2020.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing, and Controls

Question 1: *Does the Agency have any comments on the proposed list of CMC/Quality documents to be included in 3.2.R Regional Information of the BLA?*

FDA Response to Question 1: We do not agree with the proposed submission of the CMC/Quality information listed on page 12 of the Type B meeting package in Section 3.2.R Regional Information of the BLA. The following information should be included in the Section 3.2.R Regional Information:

a) The SOPs and method validation reports for the drug substance monoclonal antibody intermediate, drug linker intermediate, antibody-drug conjugate drug substance and drug product release and stability assays.

b) The master batch records and at least one of the executed batch records for the PPQ runs/lots for the drug substance monoclonal antibody intermediate, drug linker intermediate, antibody-drug conjugate drug substance and drug product.

Note that the descriptions of analytical methods and summaries of the method validation data should be included in the corresponding sections of 3.2.S.4.2 or 3.2.P.5.2 Analytical Procedures, and 3.2.S.4.3 or 3.2.P.5.3 Validation of Analytical Procedures.

Discussion: **No discussion occurred.**

Question 2: *Does the Agency agree that the intravenous (IV) compatibility and microbial challenge study designs, and that the package to be provided in the BLA are sufficient to support in-use physiochemical and microbiological attributes of the commercial product?*

FDA Response to Question 2: In general, the proposed IV compatibility study to support the commercial use of diluted drug product in IV administration appears to be reasonable. We have the following comments regarding the proposed IV compatibility study:

a) You propose to measure drug product recovery by Size Exclusion Chromatography (SEC). It is not clear whether the SEC method can accurately assess the product recovery at the proposed concentrations (b) (4) (b) (4). For instance, protein absorption to the SEC column matrix may cause low protein recovery (Reference: Arakawa T. et al. J Pharm Sci. 2010 April;99(4):1674-92). Therefore, in the BLA submission, provide method qualification data to demonstrate the proposed SEC method can accurately measure protein content at the proposed concentrations.

b) It is unclear if there is any change in the free drug content during the use of the ADCT-402 drug product. The Agency recommends including the test for free drug in the IV bag compatibility study.

c) We agree that the microbiological challenge study outlined on page 13 of the Type B meeting package is adequately designed to provide data to support transfer and storage of the reconstituted drug product diluted in 5% dextrose in the IV bag for up to 8 hours at room temperature or up to 24 hours at 2-8°C prior to patient administration. We recommend that you also include positive controls (i.e., 5% dextrose without the product) that demonstrate the viability of the challenge organisms over the duration of the test period in the study.

Discussion: **The Agency stated that overall, the plan to address the comments above appears reasonable. However, in the absence of any data at this stage, the adequacy for the exclusion of free drug linker test from in-use stability study will be assessed at the time of BLA review. The Agency recommended providing the forced degradation study data for SG-3249 linker to assess the structural integrity of the payload-linker. Regarding using the SEC method for product recovery, the Agency suggested the Sponsor to include method LOQ (limit of quantification) in the method qualification and follow the ICH Q2(R1) guideline.**

2.2. Clinical

Question 3: *Does the Agency agree with the efficacy and safety data analysis strategy as well as the proposed method of inclusion of the ISS information in the BLA?*

FDA Response to Question 3: The proposed approach appears reasonable.

Discussion: **No discussion occurred.**

For the BLA submission, ADCT anticipates that the CMC and Nonclinical modules will be complete and ready for submission in June 2020 and remaining modules of the BLA submission are anticipated to be ready for submission in September 2020. Does the Agency agree with the proposal for a rolling review submission of the complete CMC and Nonclinical modules prior to submission of the full modules 1 and 5 (Clinical) and related M2 Clinical summaries?

FDA Response to Question 12: Based on the nonclinical information provided in the meeting package, we have the following comment:

a) We refer you to the EOP1 meeting minutes from March 28, 2018, regarding the completeness of the Nonclinical modules to support the BLA submission. In this meeting, the Division agreed that fertility and carcinogenicity studies are not warranted; however, we noted that we do not have all of the information needed to waive reproductive toxicology studies. Submit data with your BLA clearly demonstrating the genotoxicity of SG3199; alternatively, you can reference data in another application if you have right to reference the data.

At this time, submission of the CMC module at an early timepoint may be acceptable, followed by submission of a complete marketing application. To be eligible for a rolling review, your product must have received fast track or breakthrough therapy designation.

Discussion: **The Agency communicated to the Sponsor that if upon review of genetic toxicology studies we conclude that the ADCT-402 and/or the payload are genotoxic, we agree that reproductive toxicology studies will not be needed per ICH S9.**

The Agency stated that in the absence of fast track or breakthrough therapy designation, the Applicant may submit only Module 3 in eCTD format via the Electronic Submission Gateway ahead of the complete application. If the Agency accepts a portion of an application, this does not necessarily mean that review will commence or proceed before the complete application is submitted.

For information on how to obtain a pre-assigned application number via the CDER NEXUS Portal, please refer to the following link: https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number. For submission-related questions please contact esub@fda.hhs.gov.

Additional Product Quality Comments

1) To facilitate the Agency's review of the drug substance monoclonal antibody intermediate, antibody drug conjugate drug substance, and drug product

manufacturing processes for ADCT-402, provide the information for process parameters and in-process control, as applicable, in the following tabular format. Please provide a separate table for each unit operation. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R.

Process Parameter/ Operating Parameter/ In-Process Control	Proven Acceptable Range/ Control Limits/ Targets[1] for Commercial Manufacturing Process	Criticality Classification[2]	Characterized Range/ Control Limits/Targets[1] tested in Process Development Studies	Manufactured Range/ Control Limits/Targets[1] used for Pivotal Clinical Study Lots	Manufactured Range/ Control Limits/Targets[1] used in Process Validation	Justification of the Proposed Commercial Acceptable Range[3]	Comment[4]

[1]As applicable.
[2]For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.
[3]This could be a brief verbal description or links to the appropriate section of the eCTD.
[4]Optional.

2) To facilitate the Agency's review of the control strategy for ADCT-402, provide information for quality attributes and process and product related impurities for the drug substance monoclonal antibody intermediate, antibody drug conjugate drug substance, and drug product in the following tabular format. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R.

Quality Attributes and Process and Product Related Impurities for CI, DS and DP	Criticality Classification[1]	Impact[2]	Source[3]	Analytical Method [4]	Proposed Control Strategy[6]	Justification of the Proposed Control Strategy[6]	Comment[7]

[1]For example, critical quality attribute or non-critical quality attribute.
[2]What is the impact of the attribute, e.g. contributes to potency, immunogenicity, safety, efficacy.
[3]What is the source of the attribute or impurity, e.g. intrinsic to the molecule, fermentation, protein A column.
[4]List all the methods used to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.
[5]List all the ways the attribute is controlled, for example, in-process testing, validated removal, release testing, stability testing.
[6]This could be a brief verbal description or links to the appropriate section of the eCTD.
[7]Optional.

Additional Product Quality Microbiology Comments

The FDA is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351a BLA submission.

All facilities should be registered with the FDA at the time of the 351a BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the antibody intermediate, the drug substance, and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

For facilities handling potent or toxic products, a risk assessment should be conducted to identify risks of cross-contamination between the products. Please refer to ICH Q9 and ISPE (2010), "Risk Based Manufacture of Pharmaceutical Products" (Risk-MaPP) for guidance. The quality risk management report and the segregations and controls implemented to mitigate the identified risks will be evaluated during the pre-license inspection. Cleaning validation limits of shared equipment should be science-based, e.g., based on Acceptable Daily Exposure (ADE) of products.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351a BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance and drug substance intermediate. The information should include, but not be limited to the following:

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).

- Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).

- Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).

- Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).

- Information and summary results from the shipping validation studies (3.2.S.2.5).

- Drug substance bioburden and endotoxin release specifications (3.2.S.4).

- Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

The CMC Drug Product section of the 351a BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA guidance for industry, *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.*[4] The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- Identification of the manufacturing areas and type of fill line (e.g., open, RABS, isolator), including area classifications.

- Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.

- Parameters for filling and capping for the vials.

- A list of all equipment and components that contact the sterile drug product (i.e., the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.

- Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.

[4] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf

- Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.

- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.

- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.

- Isolator decontamination summary data and information, if applicable.

- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.

- Information and summary results from shipping validation studies.

- Validation of capping parameters, using a container closure integrity test.

- Lyophilizer sterilization validation summary data and information.

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.

- Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.

- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b). In accordance with 21 CFR610.9, an alternative pyrogen test may be submitted in lieu of the rabbit pyrogen test (such as a Monocyte Activation Test). Full supporting test validation data should be submitted to support the use of a non-compendial pyrogen test.

- Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.

- Microbiological studies in support of the post-reconstitution and/or post-dilution storage conditions storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations that would be administered to patients, and use the label-recommended solutions and diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> *Antimicrobial Effectiveness Testing*, plus typical skin flora or species associated with hospital-borne infections. *In lieu* of this data, the product labeling should recommend that the post-reconstitution and/or post-dilution storage period is not more than 4 hours.

The CMC Drug Product section of the BLA (Section 3.2.P) for the water for injection (WFI) that is co-packaged with the drug product should contain validation data summaries to support the terminal sterilization process from a sterility assurance perspective. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA guidance for industry, *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.

The following information should be provided in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- Description of the terminal sterilization process, loading patterns, methods used to monitor and control production cycles, and the performance specifications. The autoclaves used for WFI sterilization should be identified and the requalification program should be described.

- Processing/hold time limits prior to terminal sterilization. Bioburden and endotoxin should be monitored at the end of a hold prior to terminal sterilization.

- Depyrogenation process parameters for the primary container closure system components that contact the drug product.

The following study protocols and validation data summaries for the WFI drug product should be included in Section 3.2.P.3.5:

- Depyrogenation of the drug product container closure system. Provide summary data for the three validation studies and describe the depyrogenation process revalidation program.

- In-process microbial controls and hold times prior to terminal sterilization. Three successful product intermediate hold time validation runs should be performed at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.

- Terminal sterilization process validation. Provide summary data and reports for the three validation studies. Validation summary reports should include heat distribution, heat penetration, and microbial challenge studies (including a description of the type of biological indicators used in the microbial challenge studies). Adequate justification should be provided for the validation approach taken (e.g., overkill or bioburden-based).

The following WFI product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- Container closure integrity testing. System integrity (including maintenance of the microbial barrier) should be validated initially following terminal sterilization and should be demonstrated during stability. Initial validation should be performed with units capped and terminally sterilized under worst-case processing conditions. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.