BLA 761172

BLA APPROVAL

Ridgeback Biotherapeutics, LP
Attention: Stacy McIntosh
SVP, Regulatory Affairs
3162 Commodore Plaza, Suite 3E
Coconut Grove, FL 33133-5815

Dear Ms. Mcintosh:

Please refer to your biologics license application (BLA) dated May 29, 2020, received May 29, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Ebanga (ansuvimab-zykl) 400mg/vial lyophilized powder for injection.

LICENSING

We have approved your BLA for Ebanga (ansuvimab-zykl) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Ebanga under your existing Department of Health and Human Services U.S. License No. 2162. Ebanga is indicated for the treatment of infection caused by *Zaire ebolavirus* in adult and pediatric patients, including neonates born to a mother who is RT-PCR positive for *Zaire ebolavirus* infection.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Ebanga drug substance and drug product at (b) (4). The final drug product will be labeled and packaged at (b) (4). You may label your product with the proprietary name, Ebanga, and market it as 400 mg lyophilized powder for injection in a single-dose vial.

DATING PERIOD

The dating period for Ebanga shall be 12 months from the date of manufacture when stored at 2 – 8°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) °C.

Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your 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 Ebanga 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 Ebanga, 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 & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the 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). 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, 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*

[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 at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761172**." Approval of this submission by FDA is not required before the labeling is used.

MATERIAL THREAT MEDICAL COUNTEMEASURE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a material threat medical countermeasure priority review voucher (PRV), as provided under section 565A of the Federal Food, Drug and Cosmetic Act (FDCA). This PRV has been assigned a tracking number, PRV BLA 761172. All correspondences related to this PRV should refer to this tracking number.

This PRV entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologics license application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. This PRV may be transferred by you to another sponsor of a human drug or biologic application. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the PRV was transferred. When redeeming this PRV, you should refer to this letter as an official record of the voucher. The sponsor who redeems the PRV must notify FDA of its intent to submit an application with a PRV at least 90 days before submission of the application and must include the date the sponsor intends to submit the application.

FDA has published a draft guidance, *Material Threat Medical Countermeasure Priority Review Vouchers,* at https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm592548.pdf.

This guidance, when finalized, will represent the current thinking of the FDA on this topic.

ADVISORY COMMITTEE

Your application for Ebanga was not referred to an FDA advisory committee because:

(1) the clinical trial design is acceptable

(2) the application did not raise significant safety or efficacy issues that were unexpected for a drug/biologic of this class in the intended population

(3) 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

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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 assess a signal of serious risk of emergence of Ebola virus resistance to Ebanga.

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:

3965-1 Conduct a study to identify all amino acid polymorphisms in the ansuvimab-zykl epitope (GP positions 111-119) and amino acids within 5 Angstroms from currently available *Zaire ebolavirus* (EBOV) GP sequences in public databases and perform phenotypic assessments to determine the impact that each of the substitutions have on ansuvimab-zykl neutralization using lentivirus-based particles pseudotyped with EBOV GP containing each of the substitutions. Also include EBOV GP substitutions L111I and L111F in your phenotypic analyses.

The timetable you submitted on November 2, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	09/2022
Final Report Submission:	03/2023

3965-2 Conduct a study to identify ansuvimab-zykl resistance pathways using a recombinant virus expressing *Zaire ebolavirus* (EBOV) glycoprotein (GP) to select and characterize several independent resistant isolates phenotypically and genotypically.

The timetable you submitted on November 2, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	09/2022
Final Report Submission:	03/2023

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 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.

[3] See the 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 SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3965-3 Submit all sequencing data that become available for patients who were treated with ansuvimab-zykl in the PALM and MEURI trials. Perform resistance analyses of these sequences and provide a study report discussing the approaches used and the resistance results generated.

The timetable you submitted on November 2, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2023

3965-4 Collaborate with US public health agencies, other public health agencies and local health authorities, as appropriate to design and conduct a trial to evaluate the efficacy, safety and pharmacokinetics of a higher dose of Ebanga (ansuvimab-zykl) vs. Ebanga (ansuvimab-zykl) 50 mg/kg in *Zaire ebolavirus* infected adult and pediatric patients with cycle-threshold (CT) values for nucleoprotein gene targets of less than or equal to 22 to determine if a change in dosing regimen is needed in these patients.

The timetable you submitted on November 2, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12/2022

3965-5 Submit a final report with complete, unblinded safety data for all subjects who were enrolled after interim results of the initial phase of the PALM trial and were treated with ansuvimab-zykl for *Zaire ebolavirus* infection during the PALM Extension Phase.

The timetable you submitted on November 2, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2022

3965-6 Conduct a tissue cross-reactivity study in human fetal tissues.

The timetable you submitted on November 2, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/2021
Study Completion: 09/2021
Final Report Submission: 11/2021

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

We remind you of your postmarketing commitments:

3965-7 Qualify the bioburden test method for the (b) (4) with 3 batches of product using 10 mL samples

The timetable you submitted on December 14, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2022

3965-8 Submit a feasibility study protocol for an alternative endotoxin method to mitigate low endotoxin recovery (LER) in ansuvimab drug product. If a suitable endotoxin method is not identified by March 2021, continue to develop an alternative method and provide annual progress updates to the BLA. Once a suitable endotoxin method is identified, submit the LER final study report using three lots of ansuvimab.

The timetable you submitted on November 16, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2021.

3965-9 Implement annual container closure integrity testing (CCIT) in lieu of sterility testing in the stability program for ansuvimab drug product and submit the CCIT method validation report. The CCIT method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (b) (4) .

The timetable you submitted on October 29, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2021.

3965-10 Provide data from three real-time shipments to demonstrate that shipping temperature of 2-8°C is maintained within the insulated shippers for finished drug product when exposed to summer and winter conditions.

The timetable you submitted on October 29, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2022.

3965-11 To develop and implement a fully validated virus neutralization potency assay with appropriately justified acceptance criteria for release and stability testing of ansuvimab drug substance and drug product. The method validation data and updated drug substance and drug product release and stability specifications will be reported per 21 CFR 601.12

The timetable you submitted on December 16, 2020, states that you will conduct this study according to the following schedule:

Final report submission date: 03/2022

3965-12 To conduct comprehensive compatibility and in-use stability studies to support the storage, handling, preparation, dilution scheme, and administration conditions and materials described in the ansuvimab labeling and to support the stability of drug product quality attributes during administration. The compatibility studies and in-use stability studies will include evaluation of 5% dextrose as a diluent to support the administration of drug product to neonates. The labeling will be updated based on the results from these studies. The final compatibility study data and updates to the labeling will be reported per 21 CFR 601.12

The timetable you submitted on December 2, 2020, states that you will conduct this study according to the following schedule:

Final report submission date: 03/2021

3965-13 To perform extractables/leachables studies and risk assessments to evaluate leachables from the container closure system(s) and manufacturing product conduct surfaces of ansuvimab drug substance and drug product and assess the potential impact of leachables on product quality at the end of drug product shelf-life. The analyses will be performed using drug substance and drug product lot(s) and/or representative samples (e.g. (b) (4), if justified) analyzed at appropriate time points, including at the end of drug product shelf life. Appropriate methods will be used to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals. Characterization of the potential impact on product quality will be assessed using adequate analytical methods. Complete data and the risk evaluation for the potential impact of leachables on product safety and quality will be provided in the final study report per 21 CFR 601.12.

The timetable you submitted on December 15, 2020, states that you will conduct this study according to the following schedule:

Final report submission date: 03/2022

3965-14 To conduct studies to confirm clearance of process related impurities from the commercial scale drug substance manufacturing process and a risk assessment for the residual levels of impurities on patient safety. The results from these studies and risk assessment will be provided in the final report to the BLA per 21 CFR 601.12.

The timetable you submitted on December 15, 2020, states that you will conduct this study according to the following schedule:

Final report submission date: 03/2022

3965-15 To conduct viral clearance studies using four model viruses relevant to the ansuvimab drug substance manufacturing process using a scaled down model representative of the commercial process. The analysis should consist of an assessment of virus titer before and after each step tested in two independent studies using an assay with adequate sensitivity and reproducibility. The final viral clearance report will be submitted to the BLA per 21 CFR 601.12.

The timetable you submitted on December 15, 2020, states that you will conduct this study according to the following schedule:

Final report submission date: 03/2022

3965-16 To assess the coverage of the host cell protein (HCP) assay to confirm sensitivity. The assessment should be conducted using 2D SDS-PAGE gels of the range of HCPs detected by a sensitive protein stain, such as silver stain, compared to the range detected by western blot analysis using the antibodies employed in the assays or an assay that is demonstrated to be equally or more sensitive than western blot. The approximate percentage of HCP impurities that are recognized by the HCP antibodies will be provided from an appropriate number of ansuvimab drug substance lots. The validation data and updates to the drug substance control strategy, if applicable, will be provided in the final report to the BLA per 21 CFR 601.12.

The timetable you submitted on December 16, 2020, states that you will conduct this study according to the following schedule:

Final report submission date: 03/2022

3965-17 To further characterize the potential contribution of antibody-dependent cellular cytotoxicity (ADCC) activity to the mechanism of action (MOA) of ansuvimab and to assess all accessible clinical and PPQ lots for ADCC activity. If the data confirm that ADCC activity contributes to the MOA or if ADCC activity cannot be ruled out as a potential MOA, update the control strategy to ensure that ADCC activity is adequately controlled. The final characterization study results and assay validation reports and updates to the drug substance and drug product control strategy, if applicable, will be submitted to the BLA per 21 CFR 601.12.

The timetable you submitted on December 15, 2020, states that you will conduct this study according to the following schedule:

Final report submission date: 03/2022

3965-18 To develop and implement a control strategy for the (b) (4) excipient in ansuvimab drug substance and drug product. The control strategy may include a validated (b) (4) assay with appropriately justified acceptance criteria for release and/or stability testing of ansuvimab drug substance and drug product. The updated drug substance and drug product control strategy and supporting data will be reported per 21 CFR 601.12

The timetable you submitted on December 15, 2020, states that you will conduct this study according to the following schedule:

Final report submission date: 03/2022

3965-19 To provide data confirming that the lower action limit for the critical process parameter and in-process control of drug product fill weight in section 3.2.P.3.4 supports the withdrawal of 8 mL per drug product vial following reconstitution and the concentration of drug product is within appropriate range. The final report and updates to the drug product control strategy and supporting data will be reported per 21 CFR 601.12.

The timetable you submitted on December 15, 2020, states that you will conduct this study according to the following schedule:

Final report submission date: 03/2022

Submit clinical protocols to your IND 138090 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

You may request advisory comments on proposed introductory advertising and promotional labeling. 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*.[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

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:

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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 biological products 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 Andrew Gentles, PharmD, BCPS AQ-ID, Senior Regulatory Project Manager, at (240) 402-5708 or the mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Adam Sherwat, MD
Deputy Office Director
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
- 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/

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