CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761172Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 138090

MEETING MINUTES

Ridgeback Biotherapeutics, LP
Attention: Stacy McIntosh
Head of Regulatory Affairs
3162 Commodore Plaza, Suite 3E
Coconut Grove, FL 33133-5185

Dear Ms. McIntosh:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VRC-EBOMAB092-00-AB (mAb114).

We also refer to the meeting between representatives of your firm and the FDA on January 10, 2020. The purpose of the meeting was to discuss the format and contents of the 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, call me at (240) 402-5708 or the mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Andrew Gentles, PharmD, BCPS AQ-ID
Senior Regulatory Project Manager
Antivirals Group
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

[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.

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: January 10, 2020
10:30 AM - 12:00 PM

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room 1309
Silver Spring, Maryland 20903

Application Number: 138090

Product Name: VRC-EBOMAB092-00-AB (mAB114)

Indication: Treatment of Ebola Virus Disease

Sponsor Name: Ridgeback Biotherapeutics, LP

Meeting Chair: Debra Birnkrant, MD

Meeting Recorder: Andrew Gentles, PharmD, BCPS AQ-ID

FDA ATTENDEES
Barbara Styrt, MD, MPH, Associate Director for Medical Countermeasures, Office of Infectious Diseases
Debra Birnkrant, MD, Director, Division of Antivirals (DAV)
Jeff Murray, MD, MPH, Deputy Director, DAV
Poonam Mishra, MD, MPH, Deputy Director for Safety, DAV
Linda Akunne, MPH, (Acting) Chief Project Management Staff, Division of Regulatory Operations for Infectious Diseases (DROID)
Andrew Gentles, PharmD, BCPS AQ-ID, Senior Regulatory Project Manager, DROID
Elizabeth Thompson, MS, Senior Regulatory Project Manager, DROID
Wendy Carter, DO, Clinical Team Lead, DAV
Samer El-Kamary, MD, Clinical Reviewer, DAV
Kimberly Struble, PharmD, Clinical Team Lead, DAV
Benjamin Lorenz, MD, Clinical Reviewer, DAV
Kirk Chan-Tack, MD, Clinical Reviewer, DAV
Hanan Ghantous, PhD, DABT, Nonclinical Supervisor, DAV
Christopher Ellis, PhD, Nonclinical Team Lead, DAV
David McMillan, PhD, Nonclinical Reviewer, DAV
John Dubinion, PhD, DABT, Nonclinical Reviewer, DAV

Jules O'Rear, PhD, Clinical Virology Team Lead, DAV
Eric Donaldson, PhD, Clinical Virology Reviewer, DAV
Su-Young Choi, PhD, Clinical Pharmacology Team Lead, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCPIV)
Qin Sun, PhD, Clinical Pharmacology Reviewer, OTS, OCP, DCPIV
Thamban Valappil, PhD, Statistics Team Lead, OTS, Office of Biometrics (OB), Division of Biometrics IV (DBIV)
Wen Zeng, PhD, Statistics Reviewer, OTS, OB, DBIV
Laree Tracy, MA, PhD, Statistics Reviewer, OTS, OB, DBIV
Sevan Kolejian, PharmD, MBA, Team Lead, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (DMEPA)
Rosemary Roberts, MD, Director, Counter-Terrorism and Emergency Coordination Staff,(CTECS)
Gerald Poley, MD, Medical Officer, CTECS
Kara Bertolaccini, PharmD, Regulatory Project Manager, CTECS
Frances Namuswe, PhD, Application Technical Lead (ATL) Review, Office of Biotechnology Products (OBP), Division of Biotechnology Review and Research III (DBRRIII)
Davinna Ligons, PhD, Reviewer, OBP, DBRRIII
Phillip Kronstein, MD, Team Lead, Office of Compliance, Office of Scientific Investigations (OSI), Division of Clinical Compliance Evaluation (DCCE)
Cheryl A. Grandinetti, PharmD, Office of Compliance, OSI, DCCE

SPONSOR ATTENDEES
Wendy Holman, Chief Executive Officer, Ridgeback Bio
Stacy McIntosh, Senior VP, Regulatory Affairs, Ridgeback Bio
Sabue Mulangu, MD Senior VP, Global Medical Affairs, Ridgeback Bio
Merribeth Morin, PhD Senior VP, Product Development, Ridgeback Bio
(b) (4)

BARDA
Danielle Turley, Health Scientist
James (Jim) Wangelin, Senior RQA Analyst/SME
Frank Arnold, Senior Vaccine and Biological Development Analyst/SME

CALL-IN
Wayne Holman, Co-founder, Ridgeback Biotherapeutics
(b) (4)
Mark Machalik, MSc, CMC Subject Matter Expert, BARDA

1.0 BACKGROUND

On November 7, 2019, Ridgeback Biotherapeutics, LP submitted a Type B pre-BLA meeting request which also serves as the Breakthrough Therapy-Initial Comprehensive meeting to obtain feedback on the proposed content and format of the proposed BLA submission for mAb114. mAb114 is a recombinant, fully human gamma immunoglobulin type 1 (IgG1) monoclonal antibody (mAb) targeted against the glycan cap and glycoprotein (GP1) domain of the Zaire ebolavirus (EBOV).

mAb114 was derived from peripheral blood mononuclear cells (PBMCs) from a subject who both survived the 1995 Ebolavirus outbreak in Kikwit, Democratic Republic of Congo (DRC) and maintained circulating antibodies for more than 10 years after infection. It was further developed by the National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), Vaccine Research Center (hereinafter "VRC") under the Code Name VRC-EBOMAB092-00-AB.

On January 25, 2018, VRC submitted IND 138090 to the Division of Anti-Viral Products (DAVP) and in November 2018, Ridgeback entered into a non-exclusive agreement with the VRC for mAb114. Ridgeback planned to develop mAb114 as a therapeutic treatment for EVD using the 'Animal Rule' pathway; however, based on the preliminary data from the NIAID-sponsored PALM randomized controlled trial (RCT), it was determined that the clinical data from the PALM RCT would form the primary basis to support the efficacy and safety of mAb114, in lieu of the Animal Rule pathway.

mAb114 was granted orphan-drug designation for the treatment of Ebola virus infection on May 8, 2019 and granted Breakthrough Therapy Designation on September 6, 2019. The FDA granted the request for this meeting on November 15, 2019, with a face-face meeting scheduled for January 10, 2020.

FDA sent Preliminary Comments to Ridgeback Biotherapeutics on December 18, 2019. Ridgeback responded on January 5, 2020 with a draft of their preliminary responses along with a request to discuss *Question 1a* (Nonclinical virologic & sequencing data); *Question 3a* (Resistance analyses of PALM RCT samples); *Question 3c* (ISS and ISE content and organization); *Question 6* (PI and trade name) and *Question 9a* (Indication Statement (b) (4)) in more detail. Ridgeback also provided the FDA with slides to support the upcoming meeting. A copy of Ridgeback's preliminary responses and presentation slides have been included as attachments with these meeting minutes.

2. DISCUSSION

In opening remarks, the FDA welcomed Ridgeback and stated that the Agency is committed to working with the Sponsor as it finalizes plans for submission of the BLA for mAb114. The FDA also indicated that the purpose of this meeting was to discuss the contents of a complete application and identify whether there will be any late submissions submitted for this BLA application. Ridgeback acknowledged the Agency's remarks and after introductions proceeded with their slide presentation. Below are the pertinent questions for which Ridgeback requested further discussion, along with additional topics which were discussed during the meeting.

2.1. Nonclinical

Question 1(a): Does DAVP agree that the nonclinical package presented is sufficient to support the BLA review and that no additional nonclinical studies will be required for approval?

FDA Response: The nonclinical package as described appears sufficient to support licensure at this time, but a final decision will depend on the comprehensive review of all data submitted with the BLA. We note that additional nonclinical virology studies may be required post marketing. In addition to the abbreviated study reports, please submit all available virologic and sequencing data from all NHP studies to the BLA. Data formats can be Excel files and/or text files for sequencing data. Please provide an update on our request for you to assess the neutralization activity of mAb114 for other Ebolavirus strains to better characterize the breadth of activity of mAb114 and determine EC50 values of mAb114 against multiple EBOV variants in a live virus system.

Sponsor's Response: *Ridgeback plans to include all available virologic data in the BLA. Ridgeback is in communication with the VRC regarding the raw dataset availability for the virologic data and if available, will provide an update at the face-to-face meeting.*

We plan to include the available virologic data in Module 4 of the BLA with the respective nonclinical pharmacology study reports. Does the Division agree with this placement in the backbone?

The neutralization activity of mAb114 against two EBOV strains (Makona and Mayinga) has been reported in the literature by Corti et al., 2016. Ridgeback will provide the available neutralization data from the literature in the BLA.

Sequencing data and resistance data are not available from the NHP studies and will not be included in the BLA. Sequencing data from NHP was not prioritized as there was no evidence of mAb resistance – i.e., all animals responded as expected to therapeutic doses of mAb114, with no evidence of virus rebound.

Discussion: The FDA concurred with the Sponsor's plan to place virologic data in Module 4 and asked that they provide a virologic summary in Module 2 with links to relevant study reports. FDA agreed that Excel files would be acceptable.

2.2. Clinical

Question 3(a): Does DAVP agree that the clinical package described is sufficient and that no additional clinical studies will be required prior to BLA submission and review?

FDA response: We agree that the proposed clinical package is sufficient to support submission of your planned BLA. Please provide an update on the resistance analyses of samples collected during the PALM trial and provide a timeline for when these data will be submitted to the BLA to allow for an independent assessment of resistance by the FDA.

Sponsor's Response: *Ridgeback continues to work on providing this information to FDA as soon as it becomes available. At this time, genomic epidemiological samples from the current EVD outbreak in North Kivu and Ituri provinces in DRC are being collected by the DRC MoH, NGOs (ALIMA, MSF, IMC and* (b) (4) *) and a consortium, comprised of INRB, USAMRIID, University of Nebraska,* (b) (4) *, and led by INRB. The consortium is leading the efforts to analyze the samples collected for sequence analysis.*

Selected samples, including PALM trial samples, from EVD confirmed cases have been sequenced for genomic analysis in order to describe the transmission chain of the EBOV and to characterize the dynamics of the outbreak. This sequencing is being conducted either in the field or in Kinshasa at INRB facilities. Since the outbreak is still ongoing, the current focus of the consortium is the genomic epidemiology to support the outbreak response. Summaries of sequence analysis are made available at a website: https://nextstrain.org/community/inrb-drc/ebola-nord-kivu?f_author=Mbala%20et%20al.

Performing resistance analysis will be a decision of the INRB leadership in collaboration with its partners and will certainly require analysis of sequences already produced and sequencing of new samples (pre and post treatment samples). Additional phenotypic assays (including production of mutant variants) will also be important and INRB does not have these assays in-house currently.

Based on the conversation between INRB leadership and Ridgeback, INRB is planning to perform the resistance analysis sometime after the end of the current outbreak. The exact timing still needs to be determined. We plan to communicate with the FDA to keep the Agency informed as to when the resistance data will be available.

Discussion: The sponsor informed the FDA that due to the limited resources in the current EVD outbreak, ongoing sequencing analysis is being prioritized to determine the transmission chain of EBOV cases. The Sponsor will communicate to the FDA any resistance analysis data as soon as it becomes available. It was agreed that this would likely occur after the BLA submission and will not be included in the BLA review.

The Sponsor requested clarification on submission of their draft Statistical Analysis Plan (SAP) with respect to the timing of their acceptance of the PALM RCT locked data from NIAID. The FDA acknowledged their concerns and it was agreed that the Sponsor will not accept delivery of the PALM RCT locked data until after the FDA has reviewed the Sponsor's SAP. The Sponsor indicated that a draft SAP will be submitted to the FDA for review by the end of January 2020.

Question 3(c): Does DAVP agree with Ridgeback's proposal to provide an abbreviated ISS and ISE for BLA 761172?

FDA response: It is unclear what is intended by an "abbreviated ISS and ISE"; however, it may be acceptable. Please clarify your intent for these documents. We

understand there are limitations to the available safety information for the MEURI EAP. Please provide more details regarding what is expected from the AE reporting from the EAP. In addition, in regard to the ISE, we do not agree that the data from EAP and nonclinical macaque data should be integrated with the efficacy data from the PALM. They should be presented separately within the report.

Sponsor's Response: *The Sponsor is proposing not to include an ISS in the BLA but to use Module 2.7.4 as the basis for the ISS. At this time, there is no good mechanism to integrate the safety data from the PALM, Phase 1, and MEURI trials, and therefore there would be limited usefulness in generating an ISS. Would it be acceptable to use Module 2.7.4 to fulfill the requirement for an ISS?*

Ridgeback would like to discuss the requirement for an ISE with the Division during the meeting. The Sponsor does not intend to integrate the nonclinical data with the clinical data. Furthermore, due to the differences in the clinical study designs, integration of the PALM and MEURI data is challenging. Therefore, providing integrated ISE datasets is virtually impossible. Ridgeback is proposing that we provide the efficacy data in Modules 2.6.2 and 2.7.3 and not provide an ISE. The Sponsor would provide an ISE document which would cross reference Modules 2.6.2 and 2.7.3. Would this plan for an ISE be acceptable to FDA?

Discussion: The FDA concurred with the Sponsor's proposal to use Summary documents in Modules 2.7.3 and 2.7.4 to fulfill the requirement of the ISS and ISE respectively and provide a cross reference to these modules in Module 5. The FDA reminded the Sponsor to provide a descriptive summary of all available safety data highlighting key safety findings (including but not limited to infusion reactions). The Sponsor concurred with the FDA's request and will utilize the same approach in finalizing the ISE.

FDA also asked the Sponsor about their plans to submit safety data obtained from the extension phase of the PALM RCT to support the BLA submission. Sponsor noted challenges with obtaining safety data from the extension phase of the PALM RCT but agreed to clarify the availability and type of safety data from the extension phase of the PALM RCT and to provide a safety update report within 2 months of the BLA review. The sponsor noted challenges with obtaining safety data from the extension phase of the PALM RCT but agreed to clarify the availability and type of safety data from the extension phase of the PALM RCT and to provide a safety update report within 2 months of the BLA review.

The FDA also clarified with the Sponsor that the PALM RCT is considered a covered clinical study given that Ridgeback has provided test product to support this study and this data is being relied upon to support the effectiveness of mAb114. As such, the Sponsor will need to exercise due diligence in obtaining financial disclosure information as outlined in 21 CFR 54 and submit with the BLA submission.

2.3 Administrative

Question 5: Does DAVP agree with the proposed content of Module 1 for the BLA?

FDA Response: The proposed Module 1 appears sufficient**.**

Sponsor's Response: *No further discussion required.*

Question 6: Does DAVP agree that the draft package insert could be submitted during the BLA review and is not required for the initial BLA submission?

FDA Response: Reference is made to the email communication on December 10, 2019 between Ridgeback and Andrew Gentles, Regulatory Project Manager, Division of Antivirals, where the Sponsor confirmed that the proposed package insert will be submitted in Module 1 during the initial BLA submission.

Sponsor's Response: *We propose to submit the PI before the BLA is complete. At this time, draft labeling is proposed to be submitted with the clinical modules and prior to the CMC sections. However, a trade name would not be available at the time of PI submission. Does the Division agree with this approach?*

Discussion: The Sponsor indicated it will submit SPL labeling, draft PI and non-proprietary name, annotated draft label and a proprietary name request for review with a proposed timeline of March 2020.

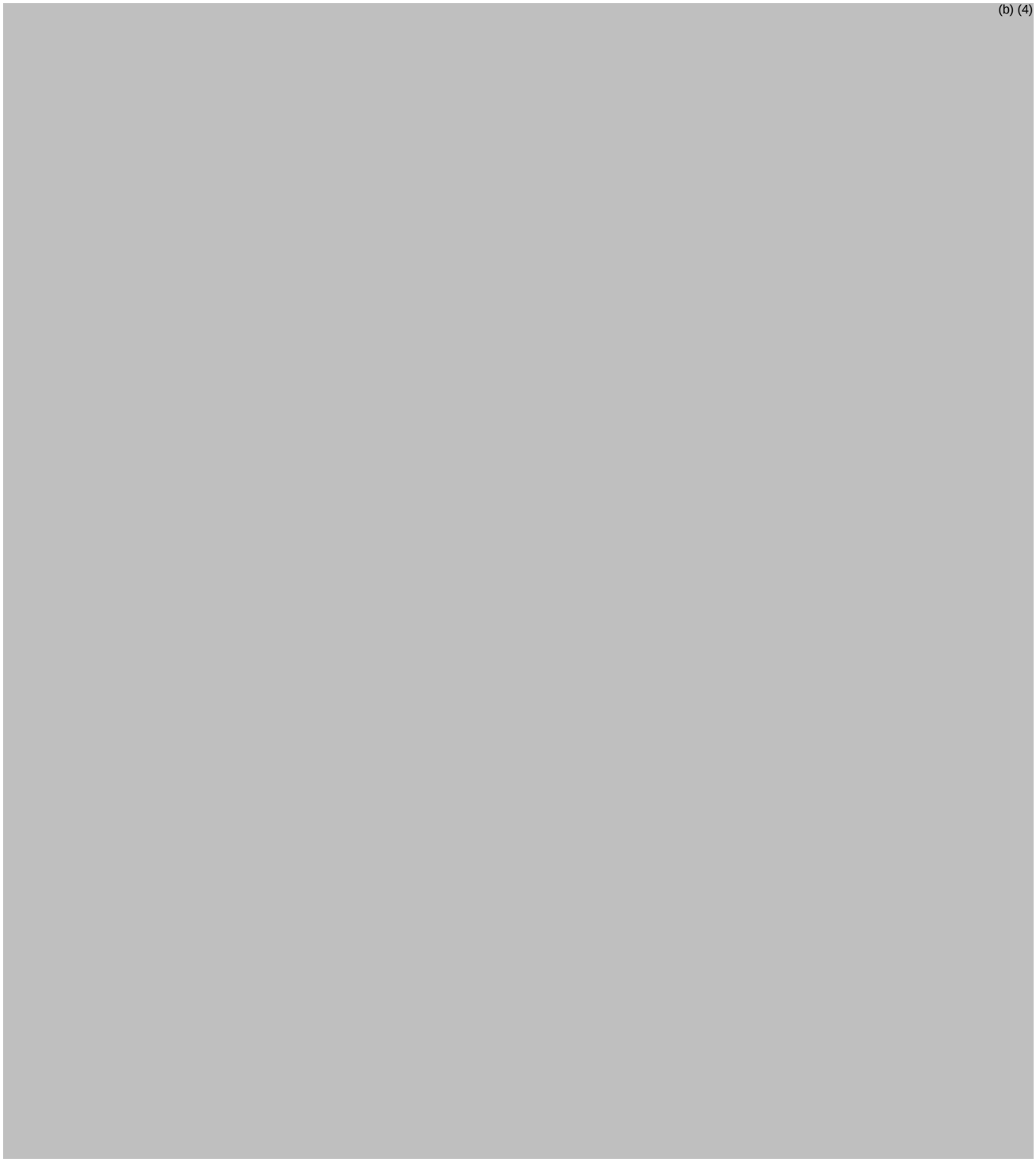
Question 9(a): Does DAVP agree that existing data will support the proposed indication?

FDA response: We agree with the proposed indication for mAb114 as a treatment of (b) (4) EBOV infection for all age groups. (b) (4)

Sponsor's Response: (b) (4)

(b) (4)

(b) (4)



DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Sponsor noted they plan to:

  - Submit complete Modules for Module 1 and 2, while Module 3 will consist of CMC information for PPQ1 and subsequent information from PPQ2 along with summary reports.
  - Submit Module 4 that will include excel spreadsheets, all study reports from toxicology and pharmacology studies
  - Submit Module 5 that will include the datasets from the EAP (treatment and PEP) and the clinical study report and datasets for the PALM RCT.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- No discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan. The FDA notes, however, that based on the currently available data, a REMS is not required at this time.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

ADDITIONAL DISCUSSION

- The Sponsor discussed some of the technical challenges in obtaining the Case Report Forms (CFRs) and asked the Agency whether it would be permissible not to submit CRFs. The Agency clarified that it does not need the original paper CRFs from the DRC, but that the PDF copies that were sent to the NIH and used for data entry into the REDCap database would suffice.

- The Sponsor asked for additional clarification from the Agency regarding its request sent on January 8, 2020 to perform a sensitivity analysis. The Agency provided additional clarification for the sensitivity analysis. FDA statisticians reassured the Sponsor that the primary analysis will be based on the entire dataset as per the pre-defined ITT population. However, sensitivity/secondary analyses should be performed to assess the consistency of results within the trial for the two stages of the randomization: the results within the first randomization conducted before the addition of the REGN arm, and the second randomization conducted after the addition of the REGN arm. Sensitivity analyses will not serve as the primary basis for determining efficacy in the PALM RCT. The Agency asked that the Sponsor discuss this request with their biostatistician and make every effort to perform the sensitivity analyses.

- The Sponsor will provide the Agency with an updated summary on the timelines and batching plan for the Rolling Review submissions. The Sponsor stated that they will provide this to the FDA within 2 weeks after this meeting. They plan to submit all nonclinical modules very soon. Module 1 is also planned for submission in this first piece.

- In addition, the Agency noted that a CMC pre-BLA submission meeting occurred on January 8, 2020. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

- The FDA requested that the BLA include a description of the real time RT-PCR assay(s) along with performance characteristics for each assay that was used to assess viral load in the PALM trial and in the EAP.

- (b) (4)

Post-meeting Addendum

We recommend that you submit an integrated immunogenicity summary report. The report should include a summary of the validation of the anti-drug antibody (ADA) screening, confirmatory, titer, and neutralization assays (if applicable), and analysis of the clinical samples. Submit the Integrated Immunogenicity Summary Report in accordance with Section VIII Documentation of the 2019 FDA Guidance for Industry: *Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection*.

3.0 PREA REQUIREMENTS

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 the treatment indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[4]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming*

[4] https://www.fda.gov/media/85061/download

of Biological Products, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

- Sponsor's plan to provide Case Report Forms (CRFs) from PALM RCT

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Plan to submit updated waves and batch submission plan for Rolling Review	Sponsor	January 31, 2020
Submit draft SAP for review	Sponsor	January 31, 2020
Submit contents of labeling and proprietary name review (PNR)	Sponsor	March 31, 2020
Submit summary Safety Update Report within 60 days into BLA review	Sponsor	TBD
Submit follow-up on CRF issues and what is planned for submission	Sponsor	As soon as possible

Submit performance data and detailed description of the methodology for the quantitative real-time RT-PCR assay used to measure subjects viral load.	Sponsor	Upon submission of the final section of the rolling BLA.

6.0 ATTACHMENTS AND HANDOUTS

Please see copy of Sponsor's preliminary responses and presentation slides that were discussed during the meeting.

26 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

ANDREW A GENTLES
01/23/2020 01:28:22 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	138090
Request Receipt Date	26 August 2019
Product	mAb114
Indication	Treatment of patients with Ebola virus infection
Drug Class/Mechanism of Action	Monoclonal Antibody (mAb) directed against Ebola virus (EBOV) glycoprotein (GP)
Sponsor	Ridgeback Biotherapeutics, LP.
ODE/Division	OAP/DAVP
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	25 October 2019

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and** will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

mAb114 is being developed for the treatment of Ebola virus infection, which is a serious and life-threatening disease, characterized by acute hemorrhagic fever, with historical case fatality rates (CFR) ranging from 25 to 90%. The CFR in the 2014-2016 West African outbreak was 63% in confirmed cases with recorded outcomes. As of 6 August 2019 in the ongoing outbreak in the North Kivu and Ituri provinces of the Democratic Republic of the Congo (DRC), there have been 2687 confirmed cases with 1772 deaths among the confirmed cases for a CFR of 66%.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.
   N/A

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Reference ID: 4493657

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

- ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐

ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐

v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b: N/A

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Reference ID: 4493657

<u>Section II:</u> If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Ebola virus is transmitted by exposure to infected bodily fluids from an infected individual through abraded skin, mucosal tissues, or through parenteral exposure. The incubation period varies between 2 and 21 days with an average period of 6-12 days. Early symptoms of Ebola virus infection include fever, myalgias, chills, and general malaise, followed by onset of gastrointestinal symptoms such as diarrhea and abdominal pain. In one study, less than 50% of patients actually developed hemorrhagic symptoms such as petechiae, conjunctival hemorrhage, epistaxis, melena, hematemesis, and shock. Patients who progress to death often develop more severe symptoms 7 to 14 days after symptom onset, while those who recover have improvement of symptoms during the same time period. Rapid viral replication is one contributor to the development of severe disease: viremia in non-survivors can be 100- to 1000-fold higher than in survivors.

mAb114 is a human IgG1 monoclonal antibody (mAb) that targets a the glycan cap and GP1 domain of EBOV glycoprotein (GP). mAb derives from a survivor of the 1995 ebolavirus outbreak in Kikwit, Democratic Republic of Congo, who maintained circulating antibody for >10 years after infection. The mAb is produced in CHO (b) (4) cells using rDNA technology. In the current outbreak in the DRC, mAb114 is one of four investigational therapeutics provided as expanded access under the World Health Organization's (WHO) ethical framework known as Monitored Emergency Use of Unregistered Interventions (MEURI).

Among the currently available investigational therapeutics, only ZMapp™ (a triple mAb cocktail, by Mapp Biopharmaceutical, Inc.) has been previously assessed in a randomized controlled clinical trial. In 2015 during the West African outbreak of EBOV, a randomized controlled trial of ZMapp plus current standard of care (cSOC) compared with cSOC alone in patients with Ebola virus disease (EVD) diagnosed by RT-PCR was conducted. ZMapp was administered at a dose of 50 mg/kg given every three days for a total of three doses. Minimum cSOC requirements included hemodynamic monitoring, IV fluids, laboratory testing, and ability to provide concomitant medications. The mortality rate was 37% (13 of 35) in patients who received the current standard of care alone and 22% (8 of 36) in patients who received ZMapp in addition to the current standard of care; however, the trial failed to meet the prespecified statistical threshold for efficacy. Based on the results of this prior study, ZMapp was selected by the DRC as the control arm for the PALM study (Protocol 19-I-0003; NCT03719586).

The PALM trial is a Phase 2/3 randomized, controlled, open-label trial designed to study the comparative safety and efficacy of investigational therapeutics in parallel arms compared to ZMapp in patients with known EBOV disease receiving optimized standard of care (oSOC). The trial was sponsored by NIH under IND-125530 and NIH has provided a letter of authorization allowing the FDA to cross-reference their IND in review of mAb114 under IND 138090. The initial protocol included three study arms: ZMapp, mAB114 and remdesivir (an IV antiviral drug, also known as GS-5734, developed by Gilead Sciences, Inc.) The trial was amended in December 2018 to include REGN-EB3, a cocktail of three recombinant human IgG1 monoclonal antibodies (mAbs): REGN3470, REGN3471 and REGN3479.

Ridgeback Therpeutics is now the Sponsor for the IND for mAB114, which recently was transferred from NIH/VRC to take over the development and manufacture of the product. mAB114 is administered as a single intravenous dose of 50mg/kg. Originally, mAB114 was produced as a lyophilized powder for injection, manugactured by (b) (4) Manufacturing was changed to the VRC pilot plant where the formulation was changed to a frozen liquid. However, after Ridgeback Therapeutics acquired mAb114, they have committed to releasing a lyophilized formulation from the original manufacturer, (b) (4)

This is an important factor for an ebola therapeutic as a lypholized powder avoids cold chain storage and distribution issues.

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The primary endpoint for comparison in the PALM trial was mortality by Day 28, and consensus for this endpoint was reached with the DRC, WHO, and FDA. Randomization was stratified by baseline RT-PCR cycle threshold (≤22.0 vs >22.0)[3], Ebola Treatment Unit (ETU) site, and outbreak. Secondary endpoints included virologic and other clinical outcomes (e.g., time to successful discharge from the ETU, mortality up to 58 days after randomization).

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

Given the challenges of conducting a trial in EVD (e.g., due to the unpredictability of the size and location of outbreaks), mAb114 was initially developed pursuant to the requirements of the Animal Rule. mAb114 has undergone nonclinical efficacy testing in four EBOV challenge studies (using 1000 pfu of Kitwit 8U EBOV strain) in nonhuman primates (NHPs) performed at USAMRIID, employing a single IV infusion of mAb114 administered 1, 5 or 6 days post-challenge. All NHPs treated with mAB114 survived and all vehicle-treated controls animals died or were euthanized.

As of 9 August 2019, the PALM trial had enrolled 681 subjects of the planned 725 subjects enrolled, but based on the independent review of interim safety and efficacy data from 499 subjects, the DSMB recommended that the PALM study be stopped early because pre-specified stopping criterion had been met by one of the products, REGN-EB3. The preliminary results in 499 study participants indicated that those individuals receiving REGN-EB3 or mAb114 had a greater chance of survival compared to those participants in the other two arms (ZMapp or remdesivir).While the remaining subjects who have been enrolled finish their final assessments (some who were randomized to ZMapp or remdesivir after the trial was halted may have had the option to receive either REGN-EB3 or mAb114), there was an adequate number of subjects assessed to demonstrate a statistically significant comparison between treatment arms. For all subjects enrolled as of June 26, 2019, the overall case-fatality for mAb114-treated EVD subjects assessed at 28 days post-treatment was 30.5% compared to the reported WHO overall case-fatality report of approximately 67% (WHO, Ebola Situation Report, 12 AUG 2019).

The Sponsors have not yet reviewed the primary unblinded data, but based on the final assessment of the DSMB, the Division agrees that the statutory requirements needed to pursue approval under the Animal Rule no longer apply.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

The Division has not considered any other biomarkers or surrogate endpoints given that clinical benefit has now been studied in a trial of reasonable size and duration using the primary clinical endpoint of mortality as shown by the results of the PALM trial.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

[3] Baseline plasma samples with a CT value calculated using nucleoprotein targets. Lower CT values (≤22.0) are inversely proportional to viral load and have been shown to predict a significantly higher risk of mortality.

There are no approved safe and effective treatments for Ebola virus infection. Standard of care is supportive and may include intravenous fluids, electrolyte monitoring and repletion, oxygen, vasopressors, antiemetics, antidiarrheals, analgesics and treatment of concomitant infections.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[4].

Regeneron has also requested BTD for REGN-EB3 based on the results of the PALM trial, as described above.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[5], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

At the time of this BTDR, only preliminary results from the PALM trial are available but demonstrate that patients receiving mAb114 or REGN-EB3 had a greater chance of survival than patients receiving ZMapp or remdesivir. The results of the PALM trial were also sufficiently compelling that the DSMB recommended immediate termination of the randomized controlled portion of the study. An extension phase of the study was subsequently implemented that does not include ZMapp and remdesivir treatment arms. The overall case fatality rate of the outbreak is reported as 67%. Compared to the approximately 50% overall CFR in ZMapp and remdesivir arms, mAB114's overall CFR was 34%. Only 11% in patients with low baseline viral load (higher CT values) in the mAb114 arm died, compared to 24% in the ZMapp arm. Updates submitted were submitted separately to IND-125530. Treatment arms have been unblinded only to the DSMB and shared with the FDA. Final data analysis is expected in late September/early October 2019. The Sponsor presented topline results available to the public.[6] Below is amended mortality rates by arm based upon the results as unblinded to the DSMB on 8 August 2019.

Table 1: Updated Mortality Rates in the PALM Study based upon the 8 August 2019 DSMB Preliminary Report (all participants had at least 10 days of follow-up)

	Case Fatality Rate	
	Overall [a]	**Low viral load [a,b]**
ZMapp	**63/129 (48.8%)**	**18/76 (23.7%)**
mAb114	**43/127 (33.9%)**	**8/74 (10.8%)**
REGN-EB3	32/112 (28.6%)	4/65 (6.2%)
Remdesivir	70/131 (53.4%)	25/77 (32.5%)

[a] Reviewer's note: cross-referencing data submitted directly to the FDA (IND-125530), these estimates are based on outcomes reported among 499 subjects, 123 of whom had vital status only available through at least 10 days from randomization as a proxy for day 28 mortality. This is a reasonable estimate because, based on prior completed reports from the other 376 subjects, 96% who died did so within 10 days of randomization.

[b] Reviewer's note: More precisely (again, cross-referencing IND-125530), these are subjects who had NP CT values >22 (as described by Boseley's article, most were likely subjects who presented within 24 hours of developing symptoms).

[4] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

[5] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

[6] Boseley S. Ebola now curable after trials of drugs in DRC, say scientists. The Guardian [newspaper on the internet]. 12 Aug 2019 [cited 12 Aug 2019]. Available from: https://www.theguardian.com/world/2019/aug/12/ebola-now-curable-after-trials-of-drugs-in-drc-say-scientists

The overall mortality rate among subjects treated with mAb114 in the PALM trial are similar to the interim rates reported from the MEURI EAP (21% (13/62 patients as of 04 January 2019; as of June 2, 2019 196 subjects were treated with mAb 114 but updated numbers have not yet been submitted).

b. Include any additional relevant information. Consider the following in your response:

The evidence from the PALM trial can be used directly to support the evidence of effectiveness and safety for a BLA. Uncontrolled data from the MEURI EAP can be used to supplement and support the cumulative safety database. With the PALM trial (n=127, with more expected to be unblinded upon the final analysis), there have been 196 patients treated under the MEURI EAP (as of June 2, 2019), and 18 healthy volunteers combined for a total of at least 341 subjects who have received the proposed dose 50 mg/kg (single intravenous infusion) of mAb114. At this time, there are no significant safety concerns. The signs and symptoms typical of infusion reactions expected with mAbs have been observed, however, are also generally consistent with those of EVD. Presence of anti-drug antibodies (ADA) has not been assessed in Ebola-infected patients. Evaluation of PK (including assessment of exposures of individual mAbs using validated assays), immunogenicity, and additional virological data (i.e. viral target epitope mapping and resistance testing) can be assessed in the post-market setting.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

The substantial improvement of mAb114 over ZMapp is obvious based on preliminary, but substantial, evidence from clinical data in the PALM trial.

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The plan is to work with Ridgeback Therapeutics to submit a traditional BLA as soon as feasible. Originally it was presumed that the BLAs would be submitted under the Animal Rule, but now that clinical data from the PALM trial are available, this approach is no longer necessary. Our intent is to expedite reviews once a BLA is submitted, and this may be facilitated by a rolling review process. Uncontrolled clinical data from the MEURI EAP will be considered to further support the clinical safety of mAb114, and NHP efficacy studies will be considered supportive of the clinical efficacy data.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation: N/A

14. List references, if any:

1. Boseley S. Ebola now curable after trials of drugs in DRC, say scientists. The Guardian [newspaper on the internet]. 12 Aug 2019 [cited 12 Aug 2019]. Available from: https://www.theguardian.com/world/2019/aug/12/ebola-now-curable-after-trials-of-drugs-in-drc-say-scientists
2. News Release from NIH/NIAID. Independent Monitoring Board Recommends Early Termination of Ebola Therapeutics Trial in DRC Because of Favorable Results with Two of Four Candidates. 12 Aug 2019 [accessed 20 Aug 2019]. Available from: https://www niaid nih.gov/news-events/independent-monitoring-board-recommends-early-termination-ebola-therapeutics-trial-drc
3. The PREVAIL II Writing Group, for the Multi-National PREVAIL II Study Team. A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection. N Engl J Med 2016;375(15):1448-56.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 3/18/19/M. Raggio

Reference ID: 4493657

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/

SAMER S EL-KAMARY
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