CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761172Orig1s000

OTHER REVIEW(S)

Memorandum (Neonatal-Perinatal Medicine Consultation)

To: Andrew Gentles, PharmD; Senior Regulatory Project Manager
Samer El-Kamary, MD, MPH; Medical Officer
DAV/OID/OND/CDER

From: Gerri R. Baer, MD
Supervisory Medical Officer, Office of Pediatric Therapeutics, OCPP/OC

Through: Susan McCune, MD
Director, Office of Pediatric Therapeutics, OCPP/OC

Date: November 22, 2020

Subject: Neonatal-Perinatal Medicine Consultation Memo for BLA 761172 EBANGA (ansuvimab-zykl) Neonatal Labeling

MATERIALS REVIEWED:

1. Consultation Request from DAV to OPT Neonatal-Perinatal Medicine; October 29, 2020 for BLA 761172
2. Proposed Labeling for EBANGA

Published Literature
The reference list is included at the end of the consultation, following the recommendations.

NEONATAL-PERINATAL MEDICINE CONSULTATION QUESTION(S):

DAV intends to label EBANGA, which is a single monoclonal antibody, for the treatment of ebolavirus infection. Specifically, EBANGA is indicated in adult and pediatric patients (including neonates born to a mother who is rt-PCR positive for ebolavirus infection) for the treatment of infection caused by *Zaire ebolavirus*. Input on wording for the following is requested:

1. Indication of including neonates and children for the treatment of infection caused by *Zaire ebolavirus*.
2. Evaluation of the proposed labeling for the dilution, infusion and flushing instructions in Section 2.3 regarding neonates and younger children. Additionally, please note that compatibility data with D5 solution is not available and therefore is not included in proposed labeling.
3. Any further labeling recommendations.

BACKGROUND:

Description of the Disease Process

In 2014, the West African Ebola virus disease (EVD) epidemic was the largest outbreak to date. Outcomes data for pregnancies affected by EVD are limited, but available information suggests a dismal prognosis for mothers, fetuses, and any live-born neonates. From the Sierra Leone outbreak in 2014-15, out of a cohort of 67 EVD-positive pregnant women, 6 live neonates were delivered, and 5 of the neonates died. (53/67 of the mothers

also died.)[1] A review of 112 documented Ebola-infected pregnancies from 1976-2015 found 13 live births, all but one of whom died in the neonatal period.[2]

Available Therapeutics

Women of childbearing age were included in the Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE). Although pregnancy was an exclusion criterion for all the rVSVΔG-ZEBOV-GP clinical trials, 84 women were inadvertently vaccinated in early pregnancy or became pregnant soon after vaccination. There were more pregnancy losses in the vaccinated group than in a non-vaccinated contemporary cohort, but the difference was not statistically significant.[3] This vaccine (Ervebo) was approved by FDA and conditionally by the European Commission in late 2019, with another vaccine in clinical trials in the Democratic Republic of the Congo (DRC) in 2020.[4]

During the 2018 outbreak in DRC, the PALM trial, a multi-center, open-label, 1:1:1:1 randomized trial of ZMapp, mAb114 (Ansuvimab), REGN-EB3, and remdesivir was conducted. This trial, sponsored by NIAID, enrolled 681 people of all ages, including pregnant women who had confirmed Ebola virus infection. In October of 2020, REGN-EB3 was approved for the treatment of Ebolavirus in all ages under the trade name INMAZEB.

The data to support the assessment of Ansuvimab were collected in the PALM trial as well as the Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) expanded access protocol (EAP; n=251) that facilitated emergency use.

Product Description and Available Study Data

Ansuvimab (EBANGA) is a recombinant fully human IgG1 monoclonal antibody that binds to *Zaire ebolavirus* glycoprotein subunit 1 (GP1).

Subjects randomized to the ansuvimab arm of the PALM study received 50 mg/kg IV as a single infusion over 1 hour. Eligibility requirements were positive RT-PCR for the nucleoprotein gene of *Zaire ebolavirus* and no investigational therapies within the prior 30 days (excluding experimental vaccines). Neonates ≤7 days of age were eligible if the mother had documented infection, including if the mother had cleared her infection but the investigator thought the neonate was likely to be infected. All patients also received standard of care, including IV fluids, daily clinical laboratory testing, correction of hypoglycemia and electrolyte imbalances, and, as indicated, broad spectrum antibiotics and antimalarials. The primary efficacy endpoint was 28-day mortality.

Secondary endpoints, comparing ansuvimab to ZMapp, included safety and tolerability, mortality rates stratified by baseline predictors of disease, mortality rates up to 58 days after randomization, time to discharge from the Ebola treatment center, time to death, time to first negative Ebola virus rt-PCR test, and time to 2 consecutive negative Ebola virus rt-PCR tests.

The CSR includes the comparison between ansivumab (n=176) and the active comparator ZMapp (n=169) from the PALM trial. In the concurrent intent-to-treat (cITT) population, 28-day mortality rates among patients treated with ansuvimab and ZMapp (active control) were 35.1% and 49.4%, respectively (p=0.008). The mortality rate at 58 days was similar to that at 28 days, and subjects treated with ansuvimab had a shorter time to negative rt-PCR than those receiving ZMapp. The mortality of patients receiving ansuvimab was similar to that of patients receiving REGN-EB3, which was approved for all ages in October 2020. There were fewer SAEs and infusion-related adverse events in subjects receiving ansuvimab than those receiving ZMapp.

In the MEURI EAP, the mortality rate was 32.3% for subjects receiving ansuvimab, with a lower mortality rate of 15.3% in subjects with lower viral loads and mortality of 63.6% in subjects with higher viral loads. Overall concurrent case fatality rate in the DRC was 66%, so the treatment represented a halving of mortality.

> ***From the Consult Request:*** *No PK data are available for any Ebola infected person. Issues regarding sample decontamination and transport prevented any assessment of PK in the PALM trial. Although we did not have PK in adults or pediatric patients, we do have efficacy (28-day mortality) from one RCT (PALM Trial) and an expanded access program (MEURI EAP). As a result, the indication will include both adults and pediatric*

patients, including neonates. EBANGA will be administered at a dose of 50 mg/kg in an intravenous infusion over 60 minutes.

The following table shows enrollment by age group in the PALM trial and the MEURI EAP. Overall, 132 subjects (31%) of the combined population were in pediatric age groups.

Subjects Treated with Ansuvimab by Age Group, PALM Trial and MEURI EAP

Age Group	PALM RCT (N=174)	MEURI EAP (N=251)	Total (N=425)
<1 month	4 (2.3%)	6 (2.4%)	10 (2.4%)
1 month to <1 year	7 (4.0%)	8 (3.2%)	15 (3.5%)
1 year to <6 years	15 (8.6%)	28 (11.2%)	43 (10.1%)
6 to <12 years	13 (7.5%)	26 (10.4%)	39 (9.2%)
12 to <18 years	15 (8.6%)	10 (4.0%)	25 (5.9%)
<18 years	54 (31.0%)	78 (31.1%)	132 (31.1%)
≥18 years	120 (69%)	173 (69%)	293 (69%)

Abbreviations: MEURI EAP, Monitored Emergency Use of Unregistered Interventions Expanded Access Protocol; N, number of subjects; PALM, PAmoja TuLinde Maisha; RCT, randomized controlled trial;

In the PALM trial, 54 of 174 subjects (31%) who received ansuvimab were <18 years of age, with the largest proportion <6 years of age (n=26). Four subjects were <1 month of age, and seven subjects were 1 month to <1 year of age. Of the 4 enrolled neonates, two died. One was 18 days old (died one day after treatment from complications of EBV disease); and one was 28 days old of age (died on Day 45 from severe malnutrition, after recovering from EBV). Overall, the mortality rate was consistent in pediatric patients < 18 years of age (37%) and adult (34%) subjects.

PALM Trial Mortality Rate

Age Group	Ansuvimab n/N (%)	ZMapp n/N (%)
<1 month	1/4 (25.0%)	0/2 (0.0%)
1 month to <1 year	2/7 (28.6%)	1/5 (20.0%
1 year to <6 years	8/15 (53.3%)	7/12 (58.3%)
6 to <12 years	4/13 (30.8%)	2/5 (40.0%)
12 to <18 years	5/15 (33.3%)	5/9 (55.6%)
<18 years	20/54 (37.0%)	15/33 (45.5%)
≥18 years	41/120 (34.2%)	68/135 (50.4%)

Abbreviations: N, number of subjects; n, number of subjects in subgroup; PALM, PAmoja TuLinde Maisha

In the MEURI EAP, the mortality rate was 34.6% (27/78) in pediatric patients compared to 31.2% (54/173) in adults. The pediatric population included six neonates and eight infants 1 month to <1 year of age. Of the 14 subjects <1 year of age, four (including two of the six neonates) died, for a mortality rate of 28.6%. Of the entire population enrolled in MEURI EAP, the mortality rate was 32.3% (81/251), similar to the results with ansuvimab in the PALM trial.

ANALYSIS/RESPONSE:

General Comments:

The multidisciplinary review team recognized the potential public health benefit of labeling EBANGA down to birth, despite the small sample size for neonates and infants. Of the 4 neonates enrolled in the RCT, 3 survived, and in the MEURI EAP there were 14 subjects under a year of age, with a mortality rate of 28%. Neonatal mortality rate in the EAP was 33% (2/6 neonates). Overall, the drug demonstrated a significant mortality benefit

over active control in the pediatric population. Although EVD largely occurs in settings where extremely low birth weight neonates cannot be resuscitated or supported, it is important to provide dosing and administration information to address all populations for which the review team feels the potential benefits of the product outweigh potential risks.

In preterm neonates, especially those less than 2 kg birth weight, clinicians must pay close attention to fluid and electrolyte balance to avoid generalized edema/anasarca, pulmonary edema, patent ductus arteriosus (PDA), chronic lung disease of prematurity, and intraventricular hemorrhage (IVH). Any preterm neonate born to a mother with Ebolavirus infection who is also infected, is already at significant risk of poor outcomes associated with inflammation, and large volumes of non-nutritive fluids are not recommended in the first days or weeks of life. In addition, glomerular filtration rate (GFR) is low at birth and increases over the first year of life, with "healthy" preterm neonates having GFR as low as 10-20 mL/min/1.73m^2 at birth.[5] Neonates cannot easily dispose of excess fluid in the setting of prematurity, critical illness and inflammation.

The daily fluid intake for extremely preterm neonates is typically maintained from 140 – 180 mL/kg day, with higher fluid intakes needed at times for neonates with significant insensible losses. Especially in the first several days of life, for example, a 0.5 kg neonate may require up to 200 mL/kg/day.

The diluents recommended in labeling are either 0.9% sodium chloride injection or Lactated Ringers injection for adults and Lactated Ringers injection for pediatric patients. For neonates, neither is optimal, but in this setting it would be acceptable to use either diluent.

Labeling Modifications:

The Sponsor's original proposed labeling (b) (4)

After input from DAV, the Sponsor revised the original labeling to separate recommendations for administration for neonates and infants from 0.5 kg – 2 kg, including the use of a syringe pump for administration, however, they retained the recommendation to flush the line with 25 mL of diluent after administration.

Table 1: EBANGA Volume, Diluent Volume and Total Infusion Volun

Weight in kg	Volume of EBANGA	Diluent Volume (mL)[a]	Final Infusion Volume (mL)
0.5 kg		2.5 mL	3 mL
1 kg		5 mL	6 mL
2 to 10 kg		10 mL	12 to 20 mL

After several labeling discussions with the Sponsor, the review team recommended the following language.

"At the end of the infusion, if a syringe pump was used, then remove the syringe and flush with 2 to 5 ml of diluent, but not to exceed the total infusion volume; and if an infusion bag was used, replace the empty bag (b) (4) and flush the line by infusing at least 25 mL of the diluent, to ensure complete product administration."

The current label contains the following:

For patients weighing 0.5 to < 2 kg:
- Use a 10 mL syringe compatible with the IV infusion pump.
- Fill the 10 mL syringe with the appropriate amount of diluent (Table 1).
- Add the calculated volume of EBANGA to the 10 mL syringe (Table 1).
- Mix the diluted solution by gentle inversion until admixed. Do not shake.

Table 1: EBANGA Volume, Diluent Volume and Total Infusion Volume by Body Weight

Weight in kg	Volume of EBANGA	Diluent Volume (mL)[a]	Final Infusion Volume (mL)	IV Administration
0.5 kg	1mL/kg	2.5 mL	3 mL	10 mL syringe compatible with IV infusion pump
1 kg		5 mL	6 mL	
2 to 10 kg		10 mL	12 to 20 mL	25 mL IV bag
11 to 25 kg		25 mL	36 to 50 mL	50 mL IV bag
26 to 50 kg		50 mL	76 to 100 mL	100 mL IV bag
51 to 100 kg		100 mL	151 to 200 mL	250 mL IV bag
101 kg and above		150 mL	251 mL and above	500 mL IV bag

[a] The recommended diluent volume ensures the final concentration of the diluted solution is approximately 8-30 (b) (4) mg/mL.

(b) (4)

Administration

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not administer if discolored or if the vial contains visible particles.
- Do not mix with or administer as an infusion with other medicinal products.
- (b) (4) Prepare the IV infusion line with 1.2 micron in-line filter extension set.
- Administer the IV infusion solution over approximately 60 minutes.
  - The diluted EBANGA IV solution can be infused via a central line or peripheral catheter. Do not administer EBANGA as an IV push or bolus.
  - Do not co-administer other drugs simultaneously through the same infusion line.
  - Infusions may be slowed or stopped if necessary, to alleviate any side effects.

(b) (4)

- At the end of the infusion, replace the empty bag or syringe and flush the line by infusing at least 25 mL of the diluent, to ensure complete product administration.

The diluent and infusion volumes listed above are appropriate for weight (and likely corresponding gestational age), and the use of a syringe pump is appropriate for patients <2 kg. The volume of the flush has not been specified for patients 0.5-<2 kg.

RECOMMENDATIONS:

1. We agree with the proposed approval and labeling for all ages and a minimum weight of 0.5 kg.
2. We appreciate the the modifications to Section 2.2 Preparation and Administration, and we agree with DAV that the label should contain language instructing practitioners that flush volume for neonates <2 kg should be limited to no more than the volume of drug administered.
3. As Lactated Ringers solution is not typically used to treat neonates, it would be helpful to understand why it is recommended as the diluent for this population. Normal saline or D5W would be an acceptable diluent for neonates in the volumes proposed.

REFERENCES:

1. Lyman M, Mpofu JJ, Soud F, et al. Maternal and perinatal outcomes in pregnant women with suspected Ebola virus disease in Sierra Leone, 2014. *Int J Gynaecol Obstet.* 2018;142(1):71-77.
2. Bebell LM, Oduyebo T, Riley LE. Ebola virus disease and pregnancy: A review of the current knowledge of Ebola virus pathogenesis, maternal, and neonatal outcomes. *Birth Defects Res.* 2017;109(5):353-362.
3. Legardy-Williams JK, Carter RJ, Goldstein ST, et al. Pregnancy Outcomes among Women Receiving rVSVΔ-ZEBOV-GP Ebola Vaccine during the Sierra Leone Trial to Introduce a Vaccine against Ebola. *Emerg Infect Dis.* 2020;26(3):541-548.
4. First Ebola vaccine approved. *Nat Biotechnol.* 2020;38(1):6.
5. Kastl JT. Renal function in the fetus and neonate - the creatinine enigma. *Semin Fetal Neonatal Med.* 2017;22(2):83-89.

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/s/

GERRI R BAER
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 09, 2020
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	BLA 761172
Product Name and Strength:	Ebanga (ansuvimab-zykl) Injection, 400 mg per vial
Applicant/Sponsor Name:	Ridgeback Biotherapeutics, LP (Ridgeback)
OSE RCM #:	2020-1125-2
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on December 2, 2020 for Ebanga. The Division of Antivirals (DAV) requested that we review the revised carton labeling for Ebanga (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to a recommendation that we made during a previous label and labeling review[a] and to address additional comment from the Office of Biotechnology Products included in the Applicant's response to labeling comments (Appendix B).

2 CONCLUSION

The Applicant revised the carton labeling to remove the statement, "(b) (4) from the principal display panel to address our previous concern. Thus, we have no additional recommendations at this time.

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[a] Vaughan, V. Label and Labeling Review Memo for Ebanga (BLA 761172). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 30 NOV 2020. RCM No.: 2020-1125-1.

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/s/

VALERIE S VAUGHAN
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SEVAN H KOLEJIAN
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 30, 2020
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	BLA 761172
Product Name and Strength:	Ebanga (ansuvimab-zykl) Injection, 400 mg per vial
Applicant/Sponsor Name:	Ridgeback Biotherapeutics, LP (Ridgeback)
OSE RCM #:	2020-1125-1
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 23, 2020 for Ebanga. The Division of Antivirals (DAV) requested that we review the revised container label and carton labeling for Ebanga (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] Additionally, included in this submission is a Dear Healthcare Provider letter (Appendix B), which we assess from a medication error perspective in this review.

2 DISCUSSION

We note that the Applicant addressed each of our previous concerns and implemented applicable recommendations. However, we note that the Applicant included the statement, "(b) (4) on the carton labeling. As presented, it is unclear if the Applicant intends to convey vial content information (b) (4) " Additionally, we note the inclusion of an error-prone trailing zero in the statement. Thus we provide recommendation for the Applicant in section 3.1

[a] Vaughan V. Label and Labeling Review for Ebanga (BLA 761172). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 3. RCM No.: 2020-1125.

to remove the error-prone trailing zero and provide clarity on what they intend to convey with the above statement.

Our evaluation of the Dear Healthcare Provider letter did not identify areas that are vulnerable to medication error.

3 CONCLUSION

The revised carton labeling is unacceptable from a medication error perspective. We provide recommendation for Application in section 3.1 below.

3.1 RECOMMENDATIONS FOR RIDGEBACK BIOTHERAPEUTICS, LP

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

A. As currently presented, it is unclear what you intend to communicate via the carton statement, "(b) (4) in the statement. Additionally, we note use of an error-prone trailing zero. We recommend revising the statement to provide clarity. (b) (4)

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 11/17/2020

To: Andrew Gentles PharmD, BCPS AQ-ID
Senior Regulatory Project Manager
Division of Antivirals (DAV)

From: Nima Ossareh, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for:
EBANGA (ansuvimab-zykl) for injection, for intravenous use

BLA: 761172

In response to DAV consult request dated June 9, 2020, OPDP has reviewed the proposed product labeling (PI) for EBANGA (ansuvimab-zykl) for injection, for intravenous use 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.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from Division of Antiviral Products (DAVP) on November 3, 2020, and are provided below.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	November 3, 2020
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	BLA 761172
Product Name, Dosage Form, and Strength:	Ebanga (ansuvimab-zykl) Injection, 400 mg per vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Ridgeback Biotherapeutics, LP (Ridgeback)
FDA Received Date:	May 29, 2020
OSE RCM #:	2020-1125
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the approval process for Ebanga (ansuvimab-zykl) for Injection, 400 mg, the Division of Antivirals (DAV) requested that we review the proposed label and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review

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

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

3 OVERALL ASSESSMENT, FINDINGS, AND RECOMMENDATIONS

Our evaluation of the U.S. Prescribing Information, Container Label, and Carton Labeling is included in Sections 3.1 and 3.2, respectively.

3.1 ASSESSMENT OF THE PRESCRIBING INFORMATION

Our evaluation of the U.S. prescribing information (USPI) received on May 29, 2020 identified areas that are vulnerable to medication error. We collaborated with the review team to revise the Dosage and Administration section to provide comment to the Applicant to address the following identified medication error concerns:

- [redacted] (b) (4) This product is intended for use by healthcare providers (HCP); therefore, we find that the preparation and administration instructions for HCP should be included in the Dosage and Administration section of the USPI.

Comments to address the above identified issues, along with additional concerns identified by the review team were communicated to the Applicant on September 16, 2020.[a]

The Applicant submitted a revised USPI, received on September 29, 2020. Our evaluation of the revised USPI identified areas vulnerable to medication error. We collaborated with the review team to provide comment to the Applicant to address the following identified medication errors:

- The dilution and administration instructions do not align with the infusion volumes described in Table 1 of the Dosage and Administration section and are not applicable to all patient weight bands listed in Table 1.
- It is unclear if the diluent volumes listed in Table 1 are intended to be added to the volume of Ebanga or if the volumes listed are intended to represent the final total volume.

Comments to address the above identified issues, along with additional concerns identified by the review team were communicated to the Applicant on October 9, 2020.[b]

The Applicant submitted a revised USPI, received on October 15, 2020. Our evaluation of the revised USPI identified areas vulnerable to medication error. We collaborated with the review team to provide comment to the Applicant to address the following identified medication errors:

- The dilution instructions do not align with the final infusion volumes described in Table 1 of the Dosage and Administration section. As presented, (b) (4) might lead to excessive waste and administration errors. We recommend the

[a] Gentles, A. FDA Communication: BLA 761172 – Labeling (response needed no later than September 29, 2020) for Ebanga. Silver Spring (MD): FDA, CDER, DAV (US); 2020 SEP 16. BLA 761172.
[b] Gentles, A. Information Request for BLA 761172. Silver Spring (MD): FDA, CDER, DAV (US); 2020 OCT 09. BLA 761172.

applicant provide detailed instructions describing how doses should be prepared, including instructions for preparing final infusion volumes less than 25 mL.

- The dilution instructions were revised from "(b) (4) " to "(b) (4) ." We are concerned that omission of the number of times to invert the IV bag will lead to inconsistent preparation by different users. We recommend the applicant specifies the number of times to invert IV bag containing the diluted solution.
- Table 1 was revised (b) (4) However, this table could be simplified to improve readability. Additionally, (b) (4) could be removed to minimize confusion (b) (4) Furthermore, the title of the fifth column, (b) (4) is misleading as this column describes the final infusion volume to be administered via IV infusion.
- (b) (4) We recommend the Applicant incorporates this information into the dilution instructions to minimize preparation errors.

Comments to address the above identified issues, along with additional concerns identified by the review team were communicated to the Applicant on October 27, 2020[c].

3.2 ASSESSMENT OF THE CONTAINER LABEL AND CARTON LABELING

Table 2 below includes the identified medication error issues with the submitted, container label and carton labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Ridgeback Biotherapeutics, LP (entire table to be conveyed to Applicant)

Container Labels, Carton Labeling, and Packaging			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	The NDC number is denoted by a placeholder.	We are unable to evaluate the NDC number.	Clarify the NDC number that has been designated for this product. Include the NDC number on both the container

[c] Gentles, A. FDA Communication: BLA 761172 – Information Request (General Protocol Overview, Labeling and PMC/PMR Communication) for Ebanga. Silver Spring (MD): FDA, CDER, DAV (US); 2020 OCT 27. BLA 761172.

			label and carton labeling. Additionally, if the carton is intended to contain more than one vial of drug product, ensure the package code (i.e., the last 2 digits of the NDC) are different between the container label and carton labeling. Lastly, ensure the linear barcode contains the NDC per 21 CFR 201.25.
2.	The nonproprietary name suffix is missing.	A distinguishable nonproprietary name suffix facilitates accurate identification of biological products by health care practitioners and patients. The non-proprietary name suffix "-zykl" was found acceptable on September 1, 2020.[d]	Ensure the final container label and carton labeling includes the nonproprietary name suffix affixed to the core nonproprietary name and is displayed on the principle display panel of the container label and carton labeling.
3.	The expiration date format is not defined.	We are unable to evaluate the expiration date format from a medication safety perspective to determine if the intended format may increase risk for deteriorated drug medication errors.	We note that your request for an exception from the requirement to include an expiration date on the container label and carton labeling of certain Lots of Ebanga is pending Agency's determination. Please note, if the exception is not granted, we will need you to clarify the expiration date format you intend to use on container label and carton labeling. Additionally, in your response clarify whether you intend to use numerical or alphabetical characters to denote the month in your proposed expiration date format.

[d] Mena-Grillasca, C. Suffix Review for Nonproprietary Name for ansuvimab (BLA 761172). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 01. OSE RCM# 2020-1166.

			If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month.
4.	A space for HCPs to write the post-reconstitution expiration date and time is not included.	According to the USPI, reconstituted vials of Ebanga should be discarded after 4 hours if not used immediately to prepare the diluted solution.	Include a space for HCPs to write the expiration date and time following reconstitution. For example: Discard after __/__/__ __:__ The "__/__/__" will prompt HCPs to write a complete date (month, day, and year) and the "__:__" will prompt HCPs to write the complete time (hour and minute) by which the reconstituted product is to be discarded.
5.	The product strength is expressed as 400 mg.	Dry powders (e.g., lyophilized powders) that must be reconstituted prior to administration should express the strength in terms of the total amount of drug per vial to prevent confusion.	Revise the strength statement to state: "400 mg per vial".
6.	(b) (4)	Dry solids (e.g., lyophilized powders) that must be reconstituted prior to administration should only list the total strength of the drug (b) (4) .	Remove "(b) (4)" from the principal display panel. Ensure the carton labeling is revised accordingly.

7.	The usual dosage statement is presented as: [redacted] (b) (4)	The usual dosage statement is inconsistent with the Prescribing Information.	Revise the "[redacted] (b) (4) "Recommended Dosage: See prescribing information."
Carton Labeling			
1.	The net quantity (i.e., # of vials per carton) statement is not included on the principle display panel.	Required per 21 CFR 201.51.	Include the net quantity statement on the principle display panel. Ensure the net quantity is expressed in terms of numerical count of vials.
2.	The carton states [redacted] (b) (4) which may cause confusion.	Discrepancy across the labeling could lead to preparation errors.	Revise the "[redacted] (b) (4) " statement accordingly.
3.	The product identifier required under the Drug Supply Chain Security Act (DSCSA) is not included on the carton.	DSCSA requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier. The DSCSA guidance on product identifiers recommends the format of the human-readable portion be located near the 2D data matrix barcode as follows: NDC: [insert NDC] SERIAL: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date]	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf
4.	Post-reconstitution expiration and storage are not included on the carton.	Information on the expiration date and post-reconstitution storage should be included to prevent administration of deteriorated drug product errors.	Include post-reconstitution expiration and storage information on the carton.

5.	Instructions for reconstitution and dilution are not included on the carton.	Instructions for reconstituting the product and the resultant concentration should be included on the carton, if space permits. Additionally, instructions for further dilution should be in included. These instructions will inform persons responsible for preparing the product what type and volume of diluent should be used for reconstitution and further dilution.	Considering including instructions for reconstitution and further dilution and the resultant concentration following reconstitution on the carton.

4 CONCLUSION

Our evaluation of the proposed Prescribing Information, container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. We provided our Prescribing Information recommendations to the Division as stated above in our review. Our container label and carton labeling comments are provided in Table 2 above. We ask that the Division convey Table 2 in its entirety to the applicant so that recommendations are implemented prior to approval of this BLA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 1 presents relevant product information for Ebanga received on October 15, 2020 from Ridgeback Biotherapeutics, LP.

Table 1. Relevant Product Information for Ebanga	
Initial Approval Date	N/A
Nonproprietary Name	ansuvimab-zykl
Indication	Indicated for use in adult and pediatric patients for the treatment of Ebola virus disease (EVD). (b) (4) .
Route of Administration	Intravenous
Dosage Form	Injection
Strength	400 mg per vial
Dose and Frequency	50 mg/kg administered as a single intravenous infusion over 60 minutes
How Supplied	Single-dose vial containing 400 mg of ansuvimab lyophilized powder per vial
Storage and Handling	Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake. Prior to reconstitution, allow EBANGA vial(s) to reach ambient temperature (15°C to 27°C [59°F to 81°F]) for approximately 20 minutes. If for any reason reconstitution cannot proceed immediately upon reaching ambient temperature, vials that have NOT been reconstituted may be kept at ambient temperature, protected from light, for no more than 24 hours. After reconstitution, the entire storage time for reconstituted solution in the vial and the diluted solution in the IV bag should be protected from light and limited to 4 hours at either ambient temperature 15°C to 27°C [59°F to 81°F]) or refrigerated at 2°C to 8°C (36°F to 46°F).
Container Closure	Clear, (b) (4) glass vial, closed with a (b) (4) rubber stopper and sealed with an aluminum seal with red matte Flip-Off top

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Ebanga labels and labeling submitted by Ridgeback Biotherapeutics, LP.

- Container label received on May 29, 2020
- Carton labeling received on May 29, 2020
- Prescribing Information (Image not shown)
    - received on May 29, 2020, available from \\CDSESUB1\evsprod\bla761172\0008\m1\us\114-labeling\draft\labeling\draft-labeling-text.pdf
    - received on September 29, 2020, available from \\CDSESUB1\evsprod\bla761172\0026\m1\us\114-labeling\draft\labeling\draft-labeling-text-tracked-changes-word-version.docx
    - received on October 15, 2020 available from \\CDSESUB1\evsprod\bla761172\0035\m1\us\114-labeling\draft\labeling\draft-labeling-text-tracked-changes-word-version.docx

G.2 Label and Labeling Images

- Container Label

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

VALERIE S VAUGHAN
11/03/2020 12:20:30 PM

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11/03/2020 12:52:10 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date of Consult Request:	July 20, 2020
From:	Division of Pediatric and Maternal Health (DPMH) Kerri-Ann Jennings, MS, BSN, RN Senior Regulatory Project Manager
To:	Division of Antivirals (DAV)
NDA Number:	BLA 761172
Drug:	Ebanga (ansuvimab-zykl)
Applicant:	Ridgeback Biotherapeutics
Indication:	Treatment of Ebola virus disease in adults and pediatrics

The Division of Antivirals (DAV) submitted a consult request to the Division of Pediatric and Maternal Health (DPMH) on July 20, 2020, requesting feedback/recommendations regarding Pediatric labeling for the above referenced BLA.

DPMH participated in internal team meetings with DAV from August 7, 2020 through October 19, 2020 to discuss the application and proposed labeling.

DPMH – Pediatrics has no further comments at this time, thus, this memorandum will close out the consult request.

DPMH Pediatric Reviewer- Ramy Abdelrahman, MD
DPMH Pediatric Team Leader- Shetarra Walker, MD, MSCR
DPMH Division Director- Lynne Yao, MD
DPMH Deputy Director- John J. Alexander, MD, MPH
DPMH RPM- Kerri-Ann Jennings, MS, BSN, RN

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/s/

KERRI-ANN JENNINGS
10/30/2020 07:27:29 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Disease, Pediatrics, Urology, and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Memorandum

Date: September 28, 2020 **Date Consulted:** July 20, 2020

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

To: Andrew Gentiles, PharmD, BCPS, Regulatory Project Manager (RPM)
Division of Antivirals (DAV)

BLA: 761172

Drug: Ebanga (ansuvimab)

Proposed Indication: Treatment of infection caused by *Zaire ebolavirus* in adult and pediatric patients

Applicant: Ridgeback Biotherapeutics

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- BLA 761172 submitted on May 29, 2020.
- DPMH PLLR Review of REGN-EB3 (atoltivimab, maftivimab, and odesivimab) BLA 761169 by Kristie Baisden, DO, dated July 31, 2020. DARRTs Reference ID: 4650020.[1]
- Applicant's response to information request (IR) submitted on September 28, 2020.

[1]The cross-reference to the REGN-EB3 (BLA 761169) consult is included to avoid duplicating background information relevant to this class of products. DPMH's recommendations for Ebanga (BLA 761172) labeling discussed below are based solely on information from literature that is not specific to a particular product.

Consult Question: DAV requests DPMH assistance with the PLLR labeling review for this original BLA.

INTRODUCTION

On May 29, 2020, the applicant, Ridgeback Biotherapeutics, submitted an original BLA for Ebanga (ansuvimab) injection. On July 20, 2020, the Division of Antivirals (DAV) consulted the Division of Pediatric and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy, Lactation,* and *Females and Males of Reproductive Potential* subsections.

BACKGROUND

Regulatory History

- On May 29, 2020, the applicant submitted an original BLA for Ebanga (ansuvimab) injection with the proposed indication of treatment of infection caused by *Zaire ebolavirus* in adult and pediatric patients.
- On May 8, 2019, Orphan Drug designation was granted.
- On September 3, 2019, Breakthrough Therapy designation was granted.
- On September 15, 2020, the Agency sent the applicant an information request (IR) for an updated review and summary of all available pregnancy cases with reported exposure to ansuvimab during the clinical development program.
- On September 28, 2020, the applicant submitted the requested information.

Drug Characteristics[2]

- *Description:* a recombinant human IgG1 monoclonal antibody (b) (4) .
- *Mechanism of action:* a monoclonal antibody (b) (4)
- *Dosage and administration:* 50 mg/kg given as a single intravenous (IV) infusion.
- *Limitations of use:* efficacy has not been established for other species of the *Ebolavirus* and *Marburgvirus* genera.
- *Contraindications:* none.
- *Warnings and Precautions:* hypersensitivity reactions.
- *Adverse Reactions:* (b) (4) tachycardia, hypotension, tachypnea, (b) (4).
- *Molecular weight:* 146,871 Daltons.
- *Pharmacokinetics (PK):* The PK of ansuvimab was evaluated in health adults only. (b) (4) . PK data are not available for *Zaire ebolavirus* infected patients.

Ebola Virus Disease (EVD) and Pregnancy

In 2014, the Center for Disease Control (CDC) published a "Guidance for Screening and Caring for Pregnant Women with Ebola Virus Disease for Healthcare Providers in U.S. Hospitals[3]." Sections relevant to this review are briefly summarized below:

[2] Ebanga (BLA 761172), proposed package insert.

[3] Center for Disease Control (CDC) Guidance for Screening and Caring for Pregnant Women with Ebola Virus Disease for Healthcare Providers in U.S. Hospitals. https://www.cdc.gov/vhf/ebola/clinicians/evd/pregnant-women.html. Accessed 7/22/20

How EVD Affects Pregnant Women

- No evidence currently exists to suggest that pregnant women are more susceptible to infection from Ebola virus (EBOV) than the general population.
- Limited evidence suggests that pregnant women are likely to be at increased risk of severe illness and death when infected with EBOV.[4]
- Pregnant women with EVD also appear to be at increased risk of fetal loss and pregnancy-associated hemorrhage. In previous outbreaks in Africa, infants born to mothers with EBV have not survived, but whether neonatal EBOV infection was the cause of death has not always been known.[5] There is only one published report of neonatal survival in an infant born to a mother with evidence of EVD infection.[6]
- EBOV can cross the placenta, and pregnant women infected with the virus will likely transmit it to the fetus. Placental tissues from patients with EVD have demonstrated EBOV antigen.[7] EBOV RNA has also been detected in amniotic fluid, fetal meconium, vaginal secretions, umbilical cord, and buccal swab samples from neonates.[8,9,10,11]

How to Treat Pregnant Women Diagnosed with EVD

- The general medical management of pregnant women with EVD should be the same as for nonpregnant adults with EVD.
- Healthcare providers should be aware that spontaneous abortion and intrapartum hemorrhage appear to be common among women with EVD, and high perinatal mortality rates among infants of women infected with EVD has been reported.[12]

Breastfeeding Recommendations for Women with Possible Ebola

- Ebola virus has been detected in samples of breast milk,[13] but no data exist about when in the course of the disease the virus appears in breast milk or when it is cleared. Therefore, women with EVD and women who recently recovered from EVD should not breastfeed.

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[4] Mupapa K, et al. Ebola hemorrhagic fever and pregnancy. *J Infec Dis* 1999;179 Suppl 1:S11-2.
[5] Jamieson DJ, Uyeki TM, Callaghan WM, Meaney-Delman D, Rasmussen SA. What obstetrician-gynecologists should know about Ebola: a perspective from the Centers for Disease Control and Prevention. *Obstet Gynecol* 2014;124:1005-1010.
[6] Dornemann J, Burzio C, Ronsse A, et al. First Newborn Baby to Receive Experimental Therapies Survives Ebola Virus Disease. *J Infect Dis* 2017;215:171-174.
[7] Muehlenbachs A, de la Rosa Vazquez O, Bausch DG, et al. Ebola Virus Disease in Pregnancy: Clinical, Histopathologic, and Immunohistochemical Findings. *J Infect Dis* 2017;215:64-69.
[8] Oduyebo T, Pineda D, Lamin M, Leung A, Corbett C, Jamieson DJ. A Pregnant Patient With Ebola Virus Disease. *Obstet Gynecol* 2015;126:1273-1275.
[9] Caluwaerts S, Fautsch T, Lagrou D, et al. Dilemmas in Managing Pregnant Women With Ebola: 2 Case Reports. *Clin Infect Dis* 2016;62:903-905.
[10] Bower H, Grass JE, Veltus E, et al. Delivery of an Ebola Virus-Positive Stillborn Infant in a Rural Community Health Center, Sierra Leone, 2015. *Am J Trop Med Hyg* 2016;94:417-419.
[11] Baggi FM, Taybi A, Kurth A, et al. Management of pregnant women infected with Ebola virus in a treatment centre in Guinea, June 2014. *Euro Surveill* 2014;19.
[12] CDC's Ebola (Ebola virus disease). Infection prevention and control recommendations for hospitalized patients with known or suspected Ebola virus disease in U.S. hospitals. Bausch DG, Towner JS, Dowell SF, et al. Assessment of the risk of Ebola virus transmission from bodily fluids and fomites. *J Infect Dis.* 2007;196 (suppl 2):S142-S147.
[13] Kamali A, Jamieson DJ, Kpaduwa J, et al. Pregnancy, Labor, and Delivery after Ebola Virus Disease and Implications for Infection Control in Obstetric Services, United States. *Emerg Infect Dis*. 2016;22(7). [Epub ahead of print.] DOI: 10.3201/eid2207.160269. http://dx.doi.org/10.3201/eid2207.160269

In February 2020, the World Health Organization (WHO) issued "Guidelines for the management of pregnant women and breastfeeding women in the context of Ebola virus disease.[14]" Sections relevant to this review are briefly summarized below:

- The Democratic Republic of Congo is currently experiencing the second largest Ebola outbreak in history,[15] following a 2014-2016 outbreak in western Africa that had an estimated 28,000 cases. Investigational treatment and vaccination trials are ongoing, but data in the context of pregnancy and breastfeeding are limited.[16,17]
- A paucity of scientific evidence exists on how to best treat pregnant or breastfeeding women with suspected or confirmed EVD. Historical reports suggest that, among women who acquire EVD during pregnancy, there is increased mortality and morbidity, and a near 100% rate of adverse pregnancy outcomes.[18,19]

Table 1: WHO Guidelines for the Management of Pregnant and Breastfeeding Women with Ebola Virus Disease (EVD)[14]

Recommendation	Recommendation category	Strength of recommendation	Quality assessment
Treatment of pregnant women with acute EVD			
1. Clinical management for all pregnant women should include optimized supportive care.	Recommended	Strong	Very low quality evidence
2. In the context of rigorous research or in accordance with the MEURI protocol, the use of the investigational therapies REGN-EB3 and mAb 114 may be offered to pregnant women with EVD.	Recommended in the context of rigorous research or specific contexts	Strong	Very low quality evidence
Infection prevention and control measures for breastfeeding women in the context of EVD			
9. Breastfeeding should be stopped if acute EVD is suspected or confirmed in lactating women or in a breastfeeding child. The child should be separated from the breastfeeding woman and provided a breastmilk substitute as needed.	Recommended	Strong	Very low quality evidence

[14] Guidelines for the management of pregnant and breastfeeding women in the context of Ebola virus disease. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
[15] Ebola in the Democratic Republic of the Congo: Health emergency update. Geneva: WHO; 2019.
[16] Edmunds J, Jarvis C. Benefits risk analysis of vaccination of pregnant women with rSVS-ZEBOV as part of expanded access programme. London School of Hygeine and Tropical Medicine; 2018.
[17] Van Griensven J, Edwards T, de Lamallerie X, Semple MG, Gallian P, Baize S, et al. Evaluation of convalescent plasma for Ebola virus disease in Guinea. NEJM. 2016; 374(1):33-42.
[18] Ebola haemorrhagic fever in Zaire, 1976. Bull. World Health Organ. 1978;56(2):271–93.
[19] Mupapa K, Mukundu W, Bwaka MA, Kipasa M, de Roo A, Kuvula K, et al. Ebola hemorrhagic fever and D

REVIEW
PREGNANCY
Nonclinical Experience[2]
Animal reproduction studies have not been conducted with ansuvimab.

Clinical Trials
Overall, 424 adult and pediatric patients with *Zaire ebolavirus* infection received Ebanga in one clinical trial (PALM) and as part of an expanded access program (EAP) during the same outbreak. Pregnant women were not excluded considering the high mortality rate associated with *Zaire ebolavirus* infection and the likelihood that there was greater risk to the fetus from severe EVD than from therapy.

PALM-Main Phase
The safety of Ebanga for the treatment of *Zaire ebolavirus* was evaluated in PALM, a multi-center, randomized controlled trial (RCT) sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and conducted in 2018-2019 in the Democratic Republic of Congo during a *Zaire ebolavirus* outbreak. A total of 173 patients (119 adults including 5 pregnant women and 54 pediatric patients) received ansuvimab 50 mg/kg IV as a single infusion and 168 patients received an investigational control. Both arms received optimized standard of care treatment. Pregnancy outcomes are summarized below in Table 2.

Table 2: Pregnancy Outcomes Following Exposure to Ansuvimab During PALM RCT (n=5)

Subject ID	**Maternal Age (years old)**	**Reported Drug Exposure**	**Timing of Exposure**	**Maternal Outcome**	**Fetal Outcome**
(b) (6)	29 y.o. Gravida 1 Para 0	Ansuvimab	2nd trimester (20 weeks gestation)	**Maternal death** 1 day after treatment	**Fetal death in utero** (no fetal movements were noted on admission prior to drug administration. The patient expelled a macerated fetus on the same day as ansuvimab infusion, suggesting the fetal loss was unrelated to treatment).
	22 y.o. Gravida 3 Para 2	Ansuvimab Cefixime Omeprazole Paracetamol	2nd trimester (26 weeks gestation)	**Maternal survival** at 58 day follow-up	**Fetal death in utero** (17 days after treatment the patient delivered a 3rd degree macerated fetus. The fetal death was reported as likely due to complications of EVD).
	20 y.o. Gravida 1 Para 0	Ansuvimab	2nd trimester (21 weeks gestation)	**Maternal death** 8 days after treatment	**Incomplete spontaneous abortion** (vaginal bleeding and abdominal pain occurred during study drug infusion. A manual curettage procedure was performed to stop genital bleeding).
	34 y.o. Gravida 6 Para 5	Ansuvimab	2nd trimester (22 weeks gestation)	**Maternal survival** at 58 day follow-up	**Fetal death in utero** (8 weeks after treatment the patient delivered a 1st degree macerated fetus with no visible malformations. The fetal death was reported as unrelated to ansuvimab).

Subject ID	Maternal Age (years old)	Reported Drug Exposure	Timing of Exposure	Maternal Outcome	Fetal Outcome
(b) (6)	28 y.o. Gravida 4 Para 3	Ansuvimab	2nd trimester (24 weeks gestation)	**Maternal survival** at 58 day follow-up	**Fetal death in utero** (25 days after treatment the patient delivered a 2nd degree macerated fetus).

Reviewer's Comment
This Reviewer agrees with the applicant's conclusions that the adverse pregnancy outcomes observed during the PALM trial are consistent with the published literature which describe a high risk of maternal mortality, miscarriage, stillbirth, and neonatal death in pregnant women with underlying EVD.[20,21]

PALM-Extension Phase
The applicant stated in their response to DPMH's IR that pregnancy data from the PALM-extension phase are currently unavailable.[22] The applicant noted this database is maintained by NIAID and currently remains open with no timeframe for when it will be locked, cleaned, and shared with industry stakeholders.

MEURI Expanded Access Protocol (EAP)
The applicant stated in their response to DPMH's IR that pregnancy data from the MEURI EAP are also currently unavailable.[22] The applicant noted this data was collected by the WHO and no pregnancy-related information has been shared despite requests for additional data. Finally, the applicant stated the WHO has not communicated an intent to share additional information nor a timeframe for any further update.

Applicant's Review of Published Literature
The applicant did not submit a literature review related to ansuvimab use during pregnancy.

DPMH's Review of Published Literature
This Reviewer performed a search in PubMed, Embase, Micromedex[23], TERIS[24], Reprotox[25], and Briggs[26] to find relevant articles related to the use of ansuvimab during pregnancy. Search terms included "Ebanga," "ansuvimab," OR "mAb114" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," OR "miscarriage." No relevant articles were identified.

[20] Black BO, Caluwaerts S, Achar J. Ebola viral disease and pregnancy. Obstet Med 2015; 8(3):108-13.
[21] Bebell LM, et al. Ebola virus disease and pregnancy-A review of the current knowledge of Ebola virus pathogenesis, maternal and neonatal outcomes. Birth Defects Res. 2017 March 15; 109(5):353-362.
[22] Applicant's response to DPMH information request (IR) submitted on September 28, 2020.
[23] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 9/18/20.
[24] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 9/18/20.
[25] Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 9/18/20.
[26] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

LACTATION

Nonclinical Experience

Animal lactation studies have not been conducted with ansuvimab.

Applicant's Review of Published Literature

The applicant did not submit a literature review related to ansuvimab use during lactation.

DPMH's Review of Published Literature

This Reviewer performed a search in *Medications and Mother's Milk*[27], LactMed[28], Micromedex[23], Reprotox[25], Briggs[26], PubMed, and Embase to find relevant articles related to the use of ansuvimab during lactation. Search terms included "Ebanga," "ansuvimab," OR "mAb114" AND "lactation" OR "breastfeeding." No relevant articles were identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience[2]

Animal fertility studies have not been conducted with ansuvimab.

Applicant's Review of Published Literature

The applicant did not submit a literature review related to ansuvimab effects on fertility.

DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, and Reprotox[25] to find relevant articles related to the use of ansuvimab and effects on fertility. Search terms included "Ebanga," "ansuvimab," OR "mAb114" AND "fertility," "contraception," "oral contraceptives," OR "infertility." No relevant articles were identified.

DISCUSSION and CONCLUSIONS

Pregnancy

Overall, available data from the 5 pregnancies identified during the PALM trial for ansuvimab are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. The high rate of maternal and fetal morbidity and mortality observed in the PALM trial are consistent with the published literature regarding the risks to pregnancy associated with underlying maternal *Zaire ebolavirus* infection.

DPMH recommends omitting the PLLR background risk statement in subsection 8.1 of labeling, because it may be misleading considering the rate of miscarriage in patients infected with *Zaire ebolavirus* is much higher than the reported rate of 15-20% in the U.S. general population. Further, DPMH recommends omitting the indication specific background risk statement in subsection 8.1 of labeling, because it is inapplicable for this product considering infection with

[27] Hale, Thomas (2020) Medication's and Mother's Milk. https://www halesmeds.com Accessed 9/18/20.

[28] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 9/18/20.

Zaire ebolavirus is life-threatening for both the mother and fetus, and treatment should not be withheld due to pregnancy.

In addition, DPMH recommends including a Clinical Consideration in Ebanga labeling that maternal, fetal, and neonatal outcomes are poor among pregnant women infected with *Zaire ebolavirus* with the majority of such pregnancies resulting in maternal death with miscarriage, stillbirth, or neonatal death. Thus, treatment should not be withheld due to pregnancy. Because ansuvimab is a human IgG1 monoclonal antibodies, DPMH also recommends including a statement in subsection 8.1 of labeling that monoclonal antibodies are known to cross the placenta to the fetus. It is unknown whether the transfer of ansuvimab provides any treatment benefit or risk to the developing fetus.

DPMH considered whether a postmarketing requirement (PMR) for a single-arm pregnancy safety study (SPSS) should be issued for Ebanga. DPMH noted *Zaire ebolavirus* affects females of reproductive potential and the limited available human data on Ebanga use in pregnant women are insufficient to evaluate for a drug-associated risk of adverse pregnancy outcomes. DPMH determined a PMR for a SPSS will not be recommended at this time because of the baseline high mortality rates in infected patients would make collection of interpretable data impracticable. However, if maternal and fetal/neonatal morbidity and mortality improves following *Zaire ebolavirus* infection and treatment with Ebanga, and the applicant or the Agency becomes aware of a potential safety concern, then a PMR study may be issued to further evaluate the concern.

DPMH also considered whether a PMR should be issued for a pharmacokinetic (PK) study in pregnant women. Collecting PK data in pregnant women would be important to confirm the appropriate dose of ansuvimab considering the life-threating nature of maternal EVD; however, multiple feasibility concerns were noted. Furthermore, the PK of ansuvimab has only been evaluated in healthy adults. No PK data are available for *Zaire ebolavirus* infected patients.

Lactation

There are no available data on the presence of ansuvimab in human milk, the effects on the breastfed infant, or the effects on milk product. Both the CDC and WHO recommend women with EVD not breastfeed due to the reported presence of Ebola virus in breast milk and the potential for postnatal transmission in the breastfed infant. Therefore, DPMH recommends subsection 8.2 of labeling include a statement that breastfeeding is not recommended.

DPMH considered whether a PMR for a lactation study should be issued for Ebanga. Because women infected with *Zaire ebolavirus* are instructed not to breastfeed due to the potential for postnatal transmission to the breastfed infant, DPMH determined a PMR for a lactation study is not recommended for Ebanga.

Females and Males of Reproduction Potential

DPMH recommends omitting subsection 8.3 of Ebanga labeling. There are no available human or animal studies evaluating the effect of ansuvimab on male or female fertility. Similarly, pregnancy testing and contraception subheadings are not applicable because there are no available data to suggest ansuvimab use is associated with embryo-fetal toxicity.

LABELING RECOMMENDATIONS
DPMH updated Highlights, subsections 8.1, 8.2, and section 17 of labeling for compliance with the PLLR (see below). DPMH discussed the below labeling recommendations with DAV at the labeling meeting on October 6, 2020. DPMH refers to the final BLA action for final labeling.

DPMH Proposed Ebanga (ansuvimab) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------USE IN SPECIFIC POPULATIONS----------
Lactation: Women infected with *Zaire ebolavirus* should be instructed not to breastfeed due to the potential for *Zaire ebolavirus* transmission. (8.2)

FULL PRESCRIBING INFORMATION
8.1 Pregnancy
Risk Summary
Zaire ebolavirus infection is life-threatening for both the mother and fetus and treatment should not be withheld due to pregnancy *(see Clinical Considerations)*. Available data from the PALM trial in which pregnant women with *Zaire ebolavirus* infection were treated with ansuvimab demonstrate the high rate of maternal and fetal/neonatal morbidity and mortality consistent with the published literature regarding the risks associated with underlying maternal *Zaire ebolavirus* infection. These data are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal/fetal outcome. Monoclonal antibodies, such as ansuvimab, are transported across the placenta as pregnancy progresses; therefore, ansuvimab has the potential to be transferred from the mother to the developing fetus. Animal reproduction studies have not been conducted with ansuvimab.

Clinical Considerations
Disease-associated maternal and/or embryo/fetal risk
Maternal, fetal, and neonatal outcomes are poor among pregnant women infected with *Zaire ebolavirus*. The majority of such pregnancies result in maternal death with miscarriage, stillbirth, or neonatal death. Treatment should not be withheld due to pregnancy.

8.2 Lactation
Risk Summary
The Centers for Disease Control and Prevention recommend that mothers with confirmed *Zaire ebolavirus* not breastfeed their infants to reduce the risk of postnatal transmission of *Zaire ebolavirus* infection.

There are no data on the presence of ansuvimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to ansuvimab are unknown.

17 PATIENT COUNSELING
Lactation
Instruct mothers with *Zaire ebolavirus* not to breastfeed because of the risk of passing *Zaire ebolavirus* to the baby *[see Use in Specific Populations (8.2)]*.

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/s/

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TAMARA N JOHNSON
09/29/2020 09:09:31 AM

Clinical Inspection Summary

Date	16 September 2020
From	Cheryl Grandinetti, Pharm.D. Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Andrew Gentles, Pharm.D., RPM Samer El-Kamary, M.D., Medical Reviewer Wendy Carter, M.D., Medical Team Leader Debra Birnkrant, MD, Division Director, Division of Antivirals (DAV)
BLA	761172
Applicant	Ridgeback Biotherapeutics
Drug	MAb114 (ansuvimab)
NME	Yes
Proposed Indication	For the treatment of infection caused by Zaire ebolavirus
Consultation Request Date	28 April 2020
Summary Goal Date	30 September 2020
Action Goal Date	30 October 2020
PDUFA Date	30 November 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four Ebola Treatment Units (ETU), Beni, Katwa, Mangina, and Butembo, and the study sponsor, the National Institute of Allergy and Infectious Disease (NIAID), were inspected in support of BLA 761172. The inspections covered one clinical trial, Protocol 19-I-0003, The PAmoja TuLinde Maisha (PALM) study. The study appears to have been conducted adequately, and the study data submitted, including the primary efficacy endpoint data, appear acceptable in support of the respective indication.

II. BACKGROUND

BLA 761172 was submitted in support of the use of MAb114 for the treatment of Zaire ebolavirus. The key study supporting the applications was the following:

- Protocol 19-I-0003, "A Multicenter, Multi-Outbreak, Randomized, Controlled, Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with Ebola Virus Disease. The PAmoja TuLinde Maisha (PALM) Study"

This was a multi-center, multi-outbreak, randomized, open-label, controlled clinical study, sponsored by the National Institute of Allergy and Infectious Disease (NIAID), evaluating 4 experimental Ebola virus disease therapies, each administered with a backbone of optimized standard of care (e.g., fluid resuscitation, hemodynamic and respiratory support, electrolyte monitoring and replacement, and administration of broad-spectrum antibiotic and antimalarial agents, as indicated). The primary objective of Protocol 19-I-0003 was to compare the mortality at 28 days in patients with Ebola virus disease who received one of three newer investigational drugs (i.e., remdesivir, MAb114, and REGN-EB3) compared to the control arm, ZMapp.

Independent Data Safety Monitoring Board (DSMB) was included to introduce new groups or allow early stopping for futility, efficacy, or safety. The protocol opened as a 3-group trial in November 2018, with REGN-EB3 added as a fourth group in Version 3.0 of the protocol dated 12 Dec 2018. On 09 Aug 2019, the DSMB recommended that patients be assigned only to the MAb114 and REGN-EB3 groups for the remainder of the trial; the recommendation was based on the results of an interim analysis that showed superiority of these groups to ZMapp and remdesivir with respect to mortality.

- *Subjects:* 681 subjects were enrolled
- *Sites*: 4 Ebola Treatment Units (ETUs) in the Democratic Republic of the Congo
- *Study Initiation and Completion Dates:* 20 Nov 2018 to 11 Oct 2019
- *Database soft lock* occurred on 5 November 2019; *database hard lock* occurred on 17 January 2020

Eligible patients were stratified [by RT-PCR cycle threshold (≤22 vs. >22), Ebola Treatment Center site, and Outbreak] and randomized (in a 1:1:1:1 ratio) to one of the following 4 treatment groups. Group assignments were placed in sequentially numbered envelopes, which were distributed to trial sites and were to be opened sequentially at the time of enrollment.

- Group 1: ZMapp
- Group 2: Remdesivir
- Group 3: mAB114 (ansuvimab)
- Group 4: REGN-EB3 [atoltivimab (REGN3470), odesivimab (REGN3471), maftivimab (REGN3479)]

The total study duration for individual subjects was 58 days (i.e., 30 days following the primary efficacy endpoint of mortality at Day 28). Clinical evaluation (including minimal/optional laboratory assessments) was to be performed within 24 hours of randomization and then on study days 1, 2, 3, 4, 5, 6, 8, 10, 14, and 28. Viral load measurements were collected at admission to the ETU and on study days 1, 2, 3, 4, 5, 6, 8, 10, 14, and 28. Ebola virus quantitative RT-PCR results using the GeneXpert (Cepheid) assay provided both the laboratory diagnosis confirmation of Ebola virus disease and established baseline viral load. Patients who agreed to extended follow-up through Day 58 to help

characterize potential late-onset symptoms, evidence of possible virologic relapse, or other clinical changes, were either seen in person or contacted via phone.

The protocol had defined minimal standards for assessment of efficacy and safety and defined the optimal scheduled assessments for site study personnel to obtain, if the site was able, for the purpose of full longitudinal data collection. However, the inability of a site to collect the full optimal frequency of assessments due to unavoidable resource limitations, and despite best efforts, did not constitute a protocol deviation.

The *primary efficacy endpoint* was the 28-day mortality rate.

Safety Assessments
Only serious adverse events (SAEs) were systematically collected during the study. Events that were considered SAEs were limited to SAEs that were not related to underlying Ebola virus disease, as determined by the investigator, or new or worsening events that were related to the study drug or to a non-Ebola condition, as it was noted that many subjects could enter the study with existing health conditions that meet the SAE criteria.

Paper Source Records
Source document for the study were paper CRFs, informed consent documents, and laboratory reports for safety labs and Ebola PCR results. Data were collected at the ETUs and transcribed onto paper case report forms (CRFs) by the delegated team members at the ETUs. Paper source documents were available for laboratory results (e.g., blood chemistry results as well as the Ebola PCR results). Blood chemistry results as well as the Ebola PCR results were transcribed onto the applicable CRFs by the delegated team members at the sites.

Rationale for Site Selection
All four ETUs, Beni, Katwa, Mangina, and Butembo, and the study sponsor , NIAID, were selected for routine inspection for these applications.

III. RESULTS (by site):

General Comments
There were 9 clinical investigators who rotated through, staffed, and supervised the conduct of the study for the 4 ETUs. Although only four of the 9 clinical investigators, Drs. Jean-Luc Biampata, Ali Dilu, Isekusu Mpinda Fiston, and Vicky Malengera, were selected to represent the 4 ETUs during the inspections to answer questions, all 9 clinical investigators equally shared oversight of the conduct of the study during their rotation working at their respective ETU.

Furthermore, because of FDA restrictions on conducting inspections in the Democratic Republic of the Congo (DRC), Drs. Biampata, Dilu, Fiston, and Malengera authorized inspections of the 4 ETUs (i.e., Beni, Katwa, Mangina, and Butembo) to be conducted at the NIAID in Bethesda, MD. NIAID provided inspectors access to the PALM Study website (that contained scanned copies of the paper case report forms), the Huddle Database (that contained scanned copies of the informed consent documents and GeneXpert source records),and the REDCap electronic data capture (EDC) system used during the conduct of the trial (that contained the case report form data).

Because the sponsor had no documented process in place for providing certified copies (via a validated process or with a dated signature) of the original paper CRFs, study personnel in the DRC and NIAID who performed data entry in the REDCap EDC system, entered data from scanned CRFs that were not certified. Therefore, during the inspection, FDA field investigators reviewed and verified the study data from these scanned copies of the paper CRFs that were not certified. Please see the NIAID inspection summary below for more information on the process for collecting the study data and scanning, emailing, and uploading scanned copies of the CRFs to the PALM Study website. French translators, provided by NIAID, were present during the inspection.

1. Jean-Luc Biampata, MD
   Protocol 19-I-0003
   Site: Beni
   Boulevard Nyamwisi
   Beni, Nord Kivu, Congo
   Inspection Dates: 10 – 14 August 2020

At this site for Protocol 19-I-0003, 337 subjects were screened, 335 were randomized [REGN-EB3 (n=72), ZMapp (n=84), MAb114 (n=89), and remdesivir (n=90)], and 196 subjects completed the study (i.e., survived to Day 58). Records reviewed included, but were not limited to, the study protocol and amendments; ethics committee submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; scanned copies of the paper source records; electronic case report forms; primary efficacy endpoint data (i.e., survival status); adverse event reporting; protocol deviations; documentation practices; and monitor logs and follow-up letters. A complete audit of the study records for 30 of the 337 subjects who were screened was conducted.

There was no evidence of under-reporting of adverse events. Survival status (i.e., obtained from scanned copies of discharge and death CRF paper source records) used to support the primary efficacy endpoint was reviewed and verified against the data listings provided by the sponsor for the 173 subjects who were randomized to ZMapp (n=84) and MAb114 (n=89). Survival status for the 90 subjects randomized to remdesivir was not reviewed. No discrepancies were noted.

Issues related to poor documentation were noted during inspection.

a) Subject (b) (6) (randomized to remdesivir) was a neonate born on (b) (6) and was screened and enrolled on (b) (6). No documentation or information was available on the mother's Ebola RT-PCR status.

Reviewer's comment: Dr. Biampata verbally stated during the inspection that the mother was positive and that she had died in the community. The community response coordinator brought the neonate to the Beni ETU.

b) For this site, the following GeneXpert testing result source records for screening and/or the first negative PCR could not be verified for the following 23 subjects because they were missing: (b) (6)

Reviewer's comment: While all GeneXpert testing result source records should have been retained per FDA regulations, the missing source records likely do not impact the reliability of the primary

efficacy endpoint data, which was the 28-day mortality rate. These missing source documents were discussed with Dr. Biampata and the sponsor during the inspection. The sponsor stated that the missing source records were attributed to incomplete file upload to the HUDDLE database due to internet or to computers in the DRC that had malfunctioned or had been returned to donors. There was no documentation available regarding any corrective and preventative action (CAPA) that was taken.

2. Ali Dilu, MD
   Protocol 19-I-0003
   Site Number: Katwa
   Quartier Katwa, Commune Musosa
   Katwa, Nord Kivu, Congo
   Inspection Dates: 10 – 14 August 2020

At this site for Protocol 19-I-0003, 46 subjects were screened, 46 were randomized [REGN-EB3 (n=10), ZMapp (n=12), MAb114 (n=12), and remdesivir (n=12)], and 27 subjects completed the study (i.e., survived to Day 58). Records reviewed included, but were not limited to, study protocol and amendments, ethics committee submissions, approvals, and correspondence, subject eligibility criteria, informed consent process and forms, scanned copies of the paper source records, electronic case report forms, primary efficacy endpoint data (i.e., survival status), adverse event reporting, protocol deviations, documentation practices, and monitor logs and follow-up letters. A complete audit of the study records for 24 of the 46 subjects who were screened was conducted.

There was no evidence of under-reporting of adverse events. Survival status (i.e., obtained from scanned copies of discharge and death CRF paper source records) used to support the primary efficacy endpoint was reviewed and verified against the data listings provided by the sponsor for the 24 subjects who were randomized to ZMapp (n=12) and MAb114 (n=12). Survival status for the 12 subjects randomized to remdesivir was not reviewed. No discrepancies were noted.

3. Isekusu Mpinda Fiston, MD
   Protocol 19-I-0003
   Site: Mangina
   Quartier Masimbembe, Commune
   Mangina, Nord Kivu, Congo
   Inspection Dates: 10 – 14 August 2020

At this site for Protocol 19-I-0003, 57 subjects were screened, 57 were randomized [REGN-EB3 (n=14), ZMapp (n=13), MAb114 (n=15), and remdesivir (n=15)] and 14 subjects completed to the study (i.e., survived to Day 58). Records reviewed included, but were not limited to, study protocol and amendments; ethics committee submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; scanned copies of the paper source records; electronic case report forms; primary efficacy endpoint data (i.e., survival status); adverse event reporting; protocol deviations; documentation practices; and monitor logs and follow-up letters. A complete audit of the study records for 26 of the 57 subjects who were screened was conducted.

There was no evidence of under-reporting of adverse events. Survival status (i.e., obtained from scanned copies of discharge and death CRF paper source records) used to support the primary efficacy endpoint was reviewed and verified against the data listings provided by the sponsor for 28 subjects

who were randomized to ZMapp (n=13) and MAb114 (n=15). Survival status for the 15 subjects randomized to remdesivir was not reviewed. No discrepancies were noted.

4. Vicky Malengera, MD
   Protocol 19-I-0003
   Site Number: Butembo
   Quartier Lumumba, C/ Kimeni
   Butembo, Nord Kivu, Congo
   Inspection Dates: 10 – 14 August 2020

At this site for Protocol 19-I-0003, 244 subjects were screened, 243 were randomized [REGN-EB3 (n=63), ZMapp (n=60), MAb114 (n=60), and remdesivir (n=60)] and 70 subjects completed the study (i.e., survived to Day 58). Records reviewed included, but were not limited to, study protocol and amendments; ethics committee submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms, scanned copies of the paper source records; electronic case report forms; primary efficacy endpoint data (i.e., survival status); adverse event reporting; protocol deviations; documentation practices; and monitor logs and follow-up letters. A complete audit of the study records for 35 of the 244 subjects who were screened was conducted.

There was no evidence of under-reporting of adverse events. Survival status (i.e., obtained from scanned copies of discharge and death CRF paper source records) used to support the primary efficacy endpoint was reviewed and verified against the data listings provided by the sponsor for 120 subjects who were randomized to ZMapp (n=60) and MAb114 (n=60). Survival status for the 60 subjects randomized to remdesivir was not reviewed. No discrepancies were noted.

5. National Institute of Allergy and Infectious Diseases (NIAID)
   Office of Clinical Research Policy and Regulatory Operations (OCRPRO)
   5601 Fishers Lane
   Bethesda, MD 20892
   Inspection Dates: 10 – 14 August 2020

The inspection of the sponsor, NIAID, focused on the control, oversight, and management of Protocol 19-I-0003. The inspection covered roles and responsibilities, organization and its personnel, registration of studies on clinicaltrials.gov, selection and monitoring of clinical investigators, selection of monitors, monitoring procedures and activities, quality management, adverse event reporting, data collection, handling, and management, record retention, financial disclosure, and test article shipping, accountability and management. Records reviewed during the inspection included vendor agreements and contracts, written standard operating procedures (SOPs), documentation of protocol deviations, validation, training, any other documentation related to the operational use of the electronic systems used in the trial (i.e., REDCap system, the PALM Study website, and the Huddle repository), adverse event reporting, drug accountability, and monitoring activities.

NIAID contracted with Leidos Biomedical Research, Inc. for clinical trial management, regulatory documentation, data management (e.g., EDC system management, including validation, CRF creation, data entry, query generation and resolution), laboratory, clinical supplies, and pharmacovigilance.

NIAID and Leidos Biomedical Research had no formal written SOPs or work instructions in place to

describe the process for scanning, emailing, and uploading the CRFs to the PALM Study website. In addition, NIAID was also unable to provide documentation that all parties involved in this process were trained. Because there was no documented process in place for providing certified scanned copies (via a validated process or with a dated signature) of the original paper CRFs, study personnel entered and reconciled the study data in REDCap and FDA field investigators verified the study data from copies of the CRFs that were not certified copies.

Reviewer's comment: During the inspection, a representative from Leidos Biomedical Research described the undocumented process that study personnel used to scan, email, and upload copies of the CRFs to the PALM Study Website as well as their documented procedure for double data entry (and reconciliation of the data) into the REDCap EDC system. Despite the lack of a written documented and validated process, and acknowledging that a process (albeit undocumented) existed for ensuring that all CRFs were scanned, emailed, and uploaded correctly and completely to the PALM Study Website, inspectors had some confidence that scanned copies of the CRFs that were reviewed during the inspection had the same information as the original CRFs

FDA field investigators noted during the inspection that some subject data for 28 subjects (subject numbers (b) (6)) were entered into REDCap while it was still in the development mode, and audit trails for these subjects were missing. NIAID explained that data managers failed to move the database into production mode at the start of trial and thus data for these subjects had to be re-entered from the scanned pdfs of the CRFs into REDCap once REDCap had been moved into production mode. Tracking any subsequent changes made to this data in REDCap between the time of initial entry in development mode and reentry in REDCap in production mode was missing.

As part of the root-cause for the missing audit trials, FDA field investigators determined that NIAID and Leidos Biomedical Research did not have any formal written SOPs in place for the operational use of electronic systems, for example, for developing, testing, and validating electronic systems and study specific eCRFs used in the trial and for finalizing and moving an EDC system (i.e., REDCap) from in development mode to in production mode. No formal validation test summary report or user acceptance testing reports were provided for REDCap or the PALM Study website.

Reviewer's comments: The missing audit trails for initial entry of data for subjects (b) (6) does not appear to have an impact on the integrity and quality of the data because copies of the source paper CRFs and other paper source records (i.e., Ebola PCR results and laboratory results, such as blood chemistry results) were available for inspectors to review. FDA inspectors did not solely rely on any data entered in REDCap when verifying the data listings provided by the applicants. The lack of written SOPs for the operational use of electronic systems used to capture critical data in the trial was discussed with NIAID during the closeout meeting. NIAID acknowledged the inspection finding and promised improvements for future trials, especially in those trials that may rely solely on electronic source data where missing audit trails would be critical to data integrity assessments.

There was under-reporting of a serious, unexpected, and suspected adverse reaction (SUSAR) of anaphylaxis and death in Subject (b) (6) (randomized to ZMapp). This death occurred on (b) (6) This SUSAR was promptly reported by the clinical investigator to the sponsor, NIAID; however, NIAID failed to report this SUSAR to FDA as a 7- or 15-day expedited IND safety report.

Reviewer's comment: The sponsor noted during the inspection that the SAE was expected as the Investigator's Brochure, Version 8.0, dated 6 November 2018, states "ZMapp, as with any other mAb treatment, has the potential to cause severe, including fatal, infusion reactions." However, this adverse reaction should have been considered unexpected because it was the first death due to infusion-related anaphylaxis. During inspection, NIAID confirmed with the manufacturers of ZMapp that the SUSAR that occurred in Subject (b) (6) *was the first case of infusion-related anaphylaxis and death associated with ZMapp. NIAID reported this SUSAR approximately 1 year later in their 2020 IND Annual Report (with no narrative and assessment being provided in the Annual Report). This isolated event was a discussion item at the end of the inspection.*

{See appended electronic signature page}

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