CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761169Orig1s000

OTHER REVIEW(S)

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)

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Date of This Review:	October 7, 2020
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	BLA 761169
Product Name, Dosage Form, and Strength:	Inmazeb (atoltivimab, maftivimab, and odesivimab-ebgn) Injection 241.7 mg/241.7 mg/241.7 mg per 14.5 mL (16.67 mg/16.67 mg/16.67 mg per mL)
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Regeneron Pharmaceuticals, Inc. (Regeneron)
FDA Received Date:	February 25, 2020
OSE RCM #:	2020-263
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Associate Director of Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

As part of the approval process for Inmazeb injection, 241.7 mg/241.7 mg/241.7 mg per 14.5 mL (16.67 mg/16.67 mg/16.67 mg per mL), the Division of Antivirals (DAV) requested that we review the proposed labels 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
Applicant's Response to Labeling Comments	F
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 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 prescribing information received on February 25, 2020 identified areas that are vulnerable to medication error. We collaborated with the review team to revise the Dosage and Administration, Dosage Forms, and How Supplied/Storage and Handling sections to address the following identified medication error concerns[a,b,c]:

- (b) (4) To minimize the risk of medication errors, we recommend that the strength presentation should be consistent across all labels and labeling components.
- A single dose of Inmazeb requires up to 31 vials to prepare a dose based on patient weight. The preparation instructions can be revised to provide clarity for the volume of Inmazeb needed per dose to aid infusion preparation and facilitate ease of healthcare providers double checking the correct dose is prepared.
- The storage recommendations following dilution are included in the Dosage and Administration section of the prescribing information but not in the How Supplied/Storage and Handling section, which could lead to storage errors if missed.

3.2 ASSESSMENT OF THE CONTAINER LABEL AND CARTON LABELING

Our evaluation of the container label and carton labeling for atoltivimab, maftivimab, and odesivimab-ebgn injection received on February 25, 2020 identified areas vulnerable to medication error. The following comments were communicated to the Applicant on August 21, 2020 [d]:

- The non-proprietary name suffix is denoted by the placeholder "-xxxx." The nonproprietary name suffix, -ebgn, was found conditionally acceptable on April 20, 2020.
- (b) (4)

[a] Moruf, A. FDA Communication: Labeling Comments for atoltivimab, odesivimab, maftivimab-ebgn. Silver Spring (MD): FDA, CDER, DAV (US); 2020 Jul 21. BLA 761169.

[b] Moruf, A. FDA Communication: Labeling Comments for atoltivimab, odesivimab, maftivimab-ebgn. Silver Spring (MD): FDA, CDER, DAV (US); 2020 AUG 13. BLA 761169.

[c] Moruf, A. FDA Communication: Labeling Comments for atoltivimab, odesivimab, maftivimab-ebgn. Silver Spring (MD): FDA, CDER, DAV (US); 2020 SEP 30. BLA 761169.

[d] Moruf, A. FDA Communication: Carton and Container Labeling Comments for atolivimab, odesivimab, maftivimab-ebgn. Silver Spring (MD): FDA, CDER, DAV (US); 2020 AUG 21. BLA 761169.

(b) (4) "241.7 mg/241.7 mg/241.7 mg per 14.5 mL (16.7 mg/16.7 mg/16.7 mg per mL)". Additionally, revise the carton labeling accordingly.

- The linear barcode is not included on the container label. The linear barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the container label and is required per 21 CFR 201.25(c)(2). Add the linear barcode to the container label. Ensure the linear barcode is oriented in a vertical position to allow the barcode to be properly scanned. Additionally, we note the presence of a 2D-matrix barcode. Ensure sufficient spacing between the linear barcode and 2D-matrix barcode to be properly scanned.
- The carton contents statement does not indicate how many vials are contained in the carton. Specifying the number of vials contained in each carton will help facilitate healthcare providers gathering the correct number of vials needed when preparing doses. Revise the carton contents statement to read as: "Carton (b) (4) one (1) single-dose vial and Prescribing Information."

On August 28, 2020, we received revised container label and carton labeling from the applicant. Our evaluation identified two areas for improvement and the following comments were communicated to the applicant on September 3, 2020[e]:

- (b) (4) 241.7 mg / 241.7 mg / 241.7 mg per 14.5 mL (16.67 mg / 16.67 mg / 16.67 mg per mL). Additionally, to improve readability on the container label and carton labeling, include spacing before and after each slash.
- Include the net quantity statement (i.e., One 14.5 mL single-dose vial) on the principal display panel of the carton labeling. Ensure that the net quantity statement appears away from the strength statement.

(b) (4)

Figure 1. Regeneron alternative proposal (Principal Display Panel, excerpt of vial).

[e] Moruf, A. FDA Communication: atoltivimab, maftivimab, and odesivimab-ebgn carton and container labeling comments. Silver Spring (MD): FDA, CDER, DAV (US); 2020 SEP 03. BLA 761169.

(b) (4)

On September 23, 2020, the Agency requested that the applicant (b) (4) express the strength as 241.7 mg of atoltivimab, 241.7 mg of maftivimab, and 241.7 mg of odesivimab per 14.5 mL (16.67 mg/16.67 mg/16.67 mg per mL).[f] To minimize the risk of medication errors, the Agency reiterated that the final strength presentation should be consistent across all label and labeling (i.e. USPI, container label, and carton labeling).

(b) (4)

On September 30, 2020, the Agency informed the applicant (b) (4) as 241.7 mg/241.7 mg/241.7 mg per 14.5 mL (16.67 mg/ 16.67 mg/ 16.67 mg per mL) for Agency review.[g]

On October 2, 2020, we received revised container label and carton labeling for review (see Appendix G). The applicant implemented our previous recommendations. We note that the expiration date is not included on the container label and carton labeling. However, we note that on October 5, 2020, the applicant was granted an exemption to the expiration date labeling requirements for the three lots of product that will be provided to the Strategic National Stockpile (SNS).[h]

4 CONCLUSION

Our evaluation of the proposed label and labeling received on October 2, 2020 determined they are acceptable from a medication error perspective. We have no additional recommendations at this time.

[f] Moruf, A. FDA Communication: atoltivimab, maftivimab, and odesivimab-ebgn carton and container labeling comments. Silver Spring (MD): FDA, CDER, DAV (US); 2020 SEP 23. BLA 761169.

[g] Moruf, A. FDA Communication: atoltivimab, maftivimab, and odesivimab-ebgn carton and container labeling comments. Silver Spring (MD): FDA, CDER, DAV (US); 2020 SEP 30. BLA 761169.

[h] Cavazzoni, P. FDA Communication: General Advice. Silver Spring (MD): FDA, CDER (US); 2020 OCT 05. BLA 761169.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Inmazeb received on October 2, 2020 from Regeneron Pharmaceuticals, Inc.

Table 4. Relevant Product Information for Inmazeb	
Initial Approval Date	N/A
Nonproprietary Name	atoltivimab, maftivimab, and odesivimab-ebgn
Indication	is indicated for the treatment of infection caused by Zaire ebolavirus in adult and pediatric patients, including neonates born to a mother who is RT-PCR positive for *Zaire ebolavirus* infection
Route of Administration	Intravenous infusion
Dosage Form	Injection
Strength	241.7 mg/241.7 mg/241.7 mg per 14.5 mL (16.67 mg/16.67 mg/16.67 mg per mL)
Dose and Frequency	INMAZEB is a combination of three human monoclonal antibodies co-formulated in a 1:1:1 ratio of atoltivimab, maftivimab, and odesivimab. The recommended dosage of INMAZEB is 50 mg of atoltivimab, 50 mg of maftivimab, and 50 mg of odesivimab per kg diluted and administered as a single intravenous infusion
How Supplied	INMAZEB (atoltivimab, maftivimab, and odesivimab-ebgn) injection is a clear to slightly opalescent and colorless to pale yellow solution. It is supplied in a carton containing one single dose vial of: • 241.7 mg of atoltivimab, 241.7 mg of maftivimab, and 241.7 mg of odesivimab per 14.5 mL (16.67 mg/16.67 mg/16.67 mg per mL) (NDC 61755-018-01)

<table>
<tr><td>Storage</td><td>Prior to dilution: Store INMAZEB vial refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.

After dilution:
INMAZEB does not contain preservatives. It is always recommended to administer intravenous medication immediately after preparation when possible. Store the diluted INMAZEB solution as specified according to Table 8 below. Do not freeze the diluted solution.

Table 8. Diluted INMAZEB Solution Storage Conditions
<table><tr><th>Diluent Used to Prepare Solution for Infusion</th><th>Diluted INMAZEB Solution Storage Conditions</th></tr><tr><td>0.9% Sodium Chloride Injection, USP</td><td>Store at room temperature up to 25°C (77°F) for no more than 8 hours or refrigerated at 2°C to 8°C (36°F to 46°F) for no more than 24 hours.</td></tr><tr><td>5% Dextrose Injection, USP or Lactated Ringer's Injection, USP</td><td>Store at room temperature up to 25°C (77°F) for no more than 4 hours or refrigerated or at 2°C to 8°C (36°F to 46°F) for no more than 4 hours.</td></tr></table></td></tr>
<tr><td>Container Closure</td><td>20 mL (b) (4) glass vial, a 20 mm (b) (4) stopper, and a 20 mm aluminum crimp seal cap with a flip-off button</td></tr>
</table>

APPENDIX F. APPLICANT'S RESPONSE TO CONTAINER LABEL AND CARTON LABELING COMMENTS

- Applicant's response to Agency's September 3, 2020 container label and carton labeling comments, received on September 11, 2020 and available at: \\CDSESUB1\evsprod\bla761169\0057\m1\us\111-info-amend\multi-mod-info-amend.pdf
- Applicant's response to Agency's September 23, 2020 information request, received on September 25, 2020 and available at: \\CDSESUB1\evsprod\bla761169\0065\m1\us\111-info-amend\multi-mod-info-amend.pdf

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,[i] along with postmarket medication error data, we reviewed the following atoltivimab, odesivimab, and maftivimab-ebgn labels and labeling submitted by Regeneron Pharmaceuticals, Inc.

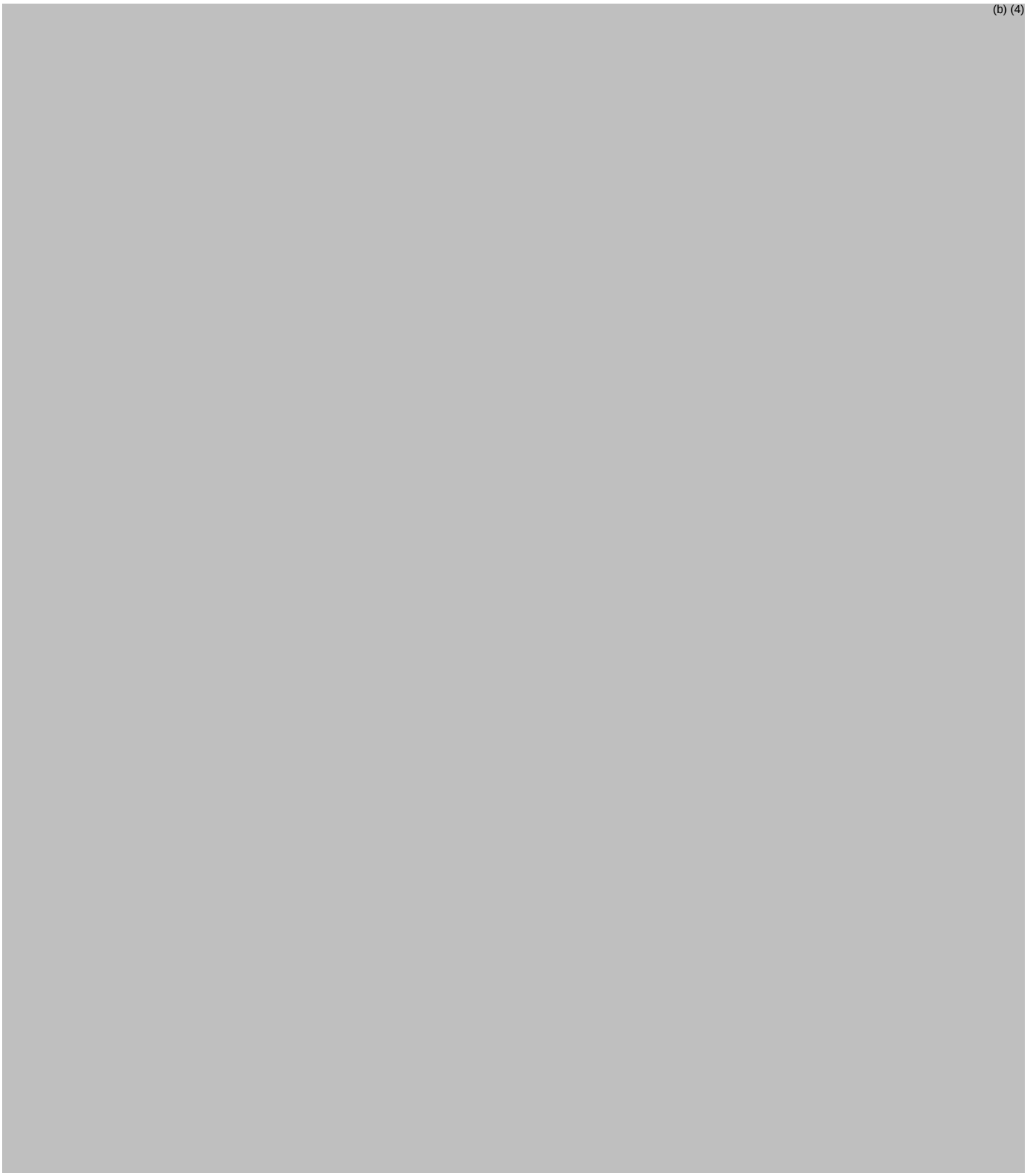
- Container label received on:
  - February 25, 2020 (image not shown)
  - August 28, 2020 (image not shown)
  - September 11, 2020 (image not shown)
  - October 2, 2020
- Carton labeling received on:
  - February 25, 2020 (image not shown)
  - August 28, 2020 (image not shown)
  - September 11, 2020 (image not shown)
  - October 2, 2020
- Prescribing Information (Image not shown) received on:
  - June 2, 2020, available from \\cdsesub1\evsprod\bla761169\0027\m1\us\114-labeling\114a-draft-label\annotated.pdf;
  - August 20, 2020, available from \\CDSESUB1\evsprod\bla761169\0048\m1\us\114-labeling\114a-draft-label\annotated.pdf; and
  - October 2, 2020, available from: \\CDSESUB1\evsprod\bla761169\0067\m1\us\114-labeling\114a-draft-label\annotated.pdf

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

G.2 Label and Labeling Images

- Container label

- Carton labeling



This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VALERIE S VAUGHAN
10/07/2020 11:13:21 PM

MISHALE P MISTRY
10/08/2020 08:52:43 AM

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

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

Memorandum

Date: 9/23/2020

To: Alicia Moruf
Regulatory Project Manager
Division of Antiviral Products (DAVP)

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

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for:
INMAZEB™ (atoltivimab, maftivimab, and odesivimab-ebgn) injection, for intravenous use

BLA: 761169

In response to DAVP consult request dated September 22, 2020, OPDP has reviewed the proposed product labeling (PI) for INMAZEB™ (atoltivimab, maftivimab, and odesivimab-ebgn) injection, for intravenous use.

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 September 18, 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.

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/

NIMA OSSAREH
09/23/2020 08:17:15 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	Alicia Moruf, Pharm.D., RPM Ben Lorenz, M.D., Medical Reviewer Kim Struble, Pharm.D., Medical Team Leader Debra Birnkrant, MD, Division Director, Division of Antivirals (DAV)
BLA #s	761169
Applicant	Regeneron Pharmaceuticals, Inc.
Drug	REGN-EB3 [atoltivimab (REGN3470), odesivimab (REGN3471), maftivimab (REGN3479)]
NME	Yes
Proposed Indication	For the treatment of infection caused by Zaire ebolavirus
Consultation Request Date	14 April 2020
Summary Goal Date	25 September 2020
Action Goal Date	25 September 2020
PDUFA Date	25 October 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 761169. 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 761169 was submitted in support of the use of REGN-EB3 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 (b) (4) 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 156 subjects who were randomized to REGN-EB3 (n=72) and ZMapp (n=84). 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* (b) (4) *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. These missing source documents were previously reported to FDA by the applicant, Regeneron.*

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 22 subjects who were randomized to REGN-EB3 (n=10) and ZMapp (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 the 27 subjects who were randomized to REGN-EB3 (n=14) and ZMapp (n=13). 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 the 123 subjects who were randomized to REGN-EB3 (n=63) and ZMapp (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 (b) (4) 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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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Memorandum

Date: July 31, 2020 **Date Consulted:** July 7, 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)

Lynne Yao, MD, Director
Division of Pediatric and Maternal Health (DPMH)

To: Alicia Moruf, Regulatory Project Manager (RPM)
Division of Antivirals (DAV)

BLA: 761169

Drug: REGN-EB3 (atoltivimab, maftivimab, and odesivimag-ebgn injection)

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

Applicant: Regeneron Pharmaceuticals

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- BLA 761169 submitted on February 25, 2020

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

INTRODUCTION

On February 25, 2020, the applicant, Regeneron Pharmaceuticals, submitted an original BLA for REGN-EB3 (atoltivimab, maftivimab, odesivimag-ebgn) injection. On July 7, 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 February 25, 2020, the applicant submitted an original BLA for REGN-EB3 (atoltivimab, maftivimab, and odesivimag-ebgn) injection with the proposed indication of treatment of infection caused by *Zaire ebolavirus* in adult and pediatric patients.
- On July 14, 2016, Orphan Drug designation was granted.
- On September 3, 2019, Breakthrough Therapy designation was granted.

Drug Characteristics[1]

- *Description:* a combination of 3 recombinant human IgG1 monoclonal antibodies (atoltivimab, maftivimab, and odesivimab) (b) (4)
- *Mechanism of action:* an antiviral drug (b) (4) *Zaire ebolavirus.* *Zaire ebolavirus* encodes a sole (b) (4) protein (b) (4) the GP, which mediates (b) (4) In addition, GP is expressed on the surface of *Zaire ebolavirus* infected host cells making it a target for antibodies that can mediate killing of these cells by antibody dependent cellular cytotoxicity and/or other effector functions. The 3 antibodies that make up the combination (b) (4) can bind the GP simultaneously.
    - Maftivimab is a neutralizing antibody that blocks entry of the virus into susceptible cells.
    - Odesivimab is a non-neutralizing antibody that induces antibody-dependent effector function through FCγRIIIa signaling when bound to its target. Odesivimab also binds to the soluble form of *Zaire ebolavirus* GP (sGP).
    - Atoltivimab combines both neutralization and FCγRIIIa signaling activities.
- *Dosage and administration:* (b) (4) as a single intravenous infusion.
- *Dosage forms and strengths:* (b) (4) in a single-dose vial.
- *Limitations of use:* efficacy has not been established for other species of the *Ebolavirus* and *Marburgvirus.*
- *Contraindications:* none
- *Warnings and Precautions:* hypersensitivity reactions
- *Adverse Reactions:* pyrexia, chills, tachycardia, and vomiting
- *Molecular weight:* atoltivimab (145 kDa), maftivimab (146 kDa), odesivimab (144 kDa)
- *Pharmacokinetics:* no pharmacokinetic (PK) data are available in patients with *Zaire ebolavirus* infection. Available PK data from healthy subjects include mean elimination half-life (days) as follows: atoltivimab (21.2), maftivimab (22.3), and odesivimab (25.3).

[1] REGN-EB3 (atoltivimab, maftivimab, and odesivimag-ebgn) BLA 761169, proposed package insert.

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 Provides in U.S. Hospitals[2]." Sections relevant to this review are briefly summarized below:

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.[3]
- 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.[4] There is only one published report of neonatal survival in an infant born to a mother with evidence of EVD infection.[5]
- 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.[6] EBOV RNA has also been detected in amniotic fluid, fetal meconium, vaginal secretions, umbilical cord, and buccal swab samples from neonates.[7,8,9,10]

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.[11]

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[2] 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

[3] Mupapa K, Mukundu W, Bwaka MA, et al. Ebola hemorrhagic fever and pregnancy. *J Infec Dis* 1999;179 Suppl 1:S11-2.

[4] 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.

[5] 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.

[6] 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.

[7] 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.

[8] 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.

[9] 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.

[10] 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.

[11] 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. Accessed May 29, 2018.Bausch DG, Towner JS,

Breastfeeding Recommendations for Women with Possible Ebola

- Ebola virus has been detected in samples of breast milk,[12] 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.

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.[13]" Sections relevant to this review are briefly summarized below:

- The Democratic Republic of Congo is currently experiencing the second largest Ebola outbreak in history,[14] 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.[15,16]
- 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.[17,18]

Table 1: WHO Guidelines for the Management of Pregnant and Breastfeeding Women with EVD[13]

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

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.

[12] 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

[13] 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.

[14] Ebola in the Democratic Republic of the Congo: Health emergency update. Geneva: WHO; 2019.

[15] 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.

[16] 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.

[17] Ebola haemorrhagic fever in Zaire, 1976. Bull. World Health Organ. 1978;56(2):271–93.

[18] Mupapa K, Mukundu W, Bwaka MA, Kipasa M, de Roo A, Kuvula K, et al. Ebola hemorrhagic fever and D

REVIEW
PREGNANCY
(b) (4)1

Animal reproduction studies have not been conducted with REGN-EB3.

Clinical Trials

Overall, 382 adult and pediatric patients (including 16 pregnant women) with EBOV infection received REGN-EB3 in one clinical trial (PALM) and an expanded access program. Pregnant women were not excluded considering the high mortality rate associated with EBOV infection and the likelihood that there was greater risk to the fetus from severe EVD than from therapy.

PALM

The safety of REGN-EB3 for the treatment of *Zaire ebolavirus* was evaluated in PALM, a multi-center, open-label, 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 154 patients (115 adult and 39 pediatric patients) received REGN-EB3 150 mg/mL IV as a single infusion and 168 patients received an investigational control. Both arms received optimized standard of care treatment. A total of 3 pregnant patients received REGN-EB3 in the PALM RCT and 5 pregnant patients received REGN-EB3 in the PALM-Extension Phase. See tables 2 and 3 below for details.

Table 2: Pregnancy Outcomes Following Exposure to RGN-EB3 During PALM RCT (n=3)

Subject ID	Maternal Age	Drug Exposure	Timing of Exposure	Maternal Outcome	Fetal Outcome
(b) (6)	29 y.o. G3P2	RGN-EB3	2nd trimester	**Alive** at day 58 follow-up	**Livebirth at 42 wks** (128 days after treatment) No congenital anomalies Placenta, umbilical cord, amniotic fluid, and salivary swab+ for Ebola by RT-PCR Newborn randomized to another investigational product (mAb114) on the day of birth. Ebola RT-PCR on the infant blood sample was negative 1 day after treatment with mAb114.
	17 y.o. G/P not reported	RGN-EB3	Unknown	**Death** on Day 2 of treatment	**Unknown** *Reviewer's Comment* *The patient presented with heavy vaginal bleeding prior to treatment. No pregnancy information was available.*
	23 y.o. G4P3	Zmapp on Day 1 and Day 8, then REGN-EB3 on Day 8	1st trimester	**Alive** at Day 58 follow-up	**Fetal death in utero at 16 wks** (Day 96 after treatment. Event reported as a non-treatment-emergent serious adverse event.

Table 3: Pregnancy Outcomes Following Exposure to RGN-EB3 During PALM-Extension Phase (n=5)

Subject ID	Maternal Age	Drug Exposure	Timing of Exposure	Maternal Outcome*	Fetal Outcome
(b) (6)	30 y.o. G6P5	REGN-EB3	2nd trimester (27 wks)	**Unknown**	**Pregnancy terminated due to fetal distress** (Day 3). Fetus with second degree maceration. *Reviewer's Comment* *The timing of the fetal loss in this case is unclear. Published literature suggest that assessing the degree of fetal maceration is not a reliable predictor of the amount of time before a fetal death occurred.*[19]
	35 y.o. G5P4	REGN-EB3	2nd trimester	**Unknown**	**Premature birth at 29 wks** (Day 13). **Neonatal death** 30 min after birth despite resuscitation. Weight: 1200 grams, Apgars 3/2. No congenital anomalies.
	23 y.o. G1P0	REGN-EB3	3rd trimester (29 wks)	**Unknown**	**Term livebirth at 39 wks** (Day 69). Weight: 2900 grams, Apgars 9/10. No congenital anomalies. PCR of breast milk and placenta + for EVD, but maternal blood, umbilical cord, and newborns blood negative.
	28 y.o. G3P2	REGN-EB3	1st trimester (9 wks)	**Unknown**	**Pregnancy terminated** (Day 3)
	40 y.o. G6P5	REGN-EB3	3rd trimester (35 wks)	**Unknown**	**Term Livebirth at 40 wks** (Day 44). Newborn small for gestational age, Apgars 9/8. No congenital anomalies. **Neonatal death at 48 hours** after delivery due to respiratory distress.

*Per the NIAID, mortality data from the PALM extension phase will not be shared with any third party until completion of the study. Thus, maternal outcomes were not available in the applicant's 60-day-safety-update report.

Reviewer's Comment

This Reviewer agrees with the applicant's conclusions that the pregnancy outcomes from both the PALM RCT main phase and extension phase 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]

[19] Gold KJ, et al. Assessment of "fresh" versus "macerated" as accurate markers of time since intrauterine fetal demise in low-income countries. Int J Gynaecol Obstet. 2014 Jun:125(3):223-227.

[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.

Expanded Access Program (EAP)
An EAP during the same *Zaire ebolavirus* outbreak was given to 228 patients (190 adults and 38 pediatric patients). A total of 8 pregnant patients received REGN-EB3 through the EAP. See Table 4 below for details.

Table 4: Pregnancy Outcomes Following Exposure to RGN-EB3 Through EAP (n=8)

Subject ID	Maternal Age	Drug Exposure	Timing of Exposure	Maternal Outcome*	Fetal Outcome
(b) (6)	30 y.o.	REGN-EB3	1st trimester (3 months)	**Alive** and discharged at Day 20	**Spontaneous abortion** treated with curettage on Day 2 *Reviewer's Comment The patient presented with vaginal bleeding which suggests the miscarriage may have been in progress prior to treatment.*
	20 y.o.	REGN-EB3	1st trimester (3 months)	**Death** on Day 1 of treatment	**Spontaneous abortion** reported within 24hrs before maternal death, manually evacuated.
	25 y.o.	REGN-EB3	1st trimester (11 weeks)	**Death** on Day 2 of treatment	**Spontaneous abortion** prior to treatment.
	20 y.o.	REGN-EB3	1st trimester (10 weeks)	**Alive** and discharged at Day 16	**Unknown**
	23 y.o.	REGN-EB3	Unknown	**Death** on Day 5 of treatment	**Unknown**
	23 y.o.	REGN-EB3	1st trimester (2 months)	**Alive** and discharged Day 17	**Unknown**
	18 y.o.	REGN-EB3	2nd trimester (7 months)	**Death** on Day 2 of treatment	**Intrauterine fetal demise** (occurred prior to treatment)
	20 y.o.	REGN-EB3	1st trimester (3 months)	**Death** on Day 3 of treatment	**Intrauterine fetal demise** (occurred post-treatment; uterine evacuation performed on unknown date)

Applicant's Review of Published Literature
The applicant did not submit a literature review related to REGN-EB3 use during pregnancy.

DPMH's Review of Published Literature
This Reviewer performed a search in PubMed, Embase, Micromedex[22], TERIS[23], Reprotox[24], and Briggs[25] to find relevant articles related to the use of REGN-EB3 during

[22] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 7/22/20.
[23]TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 7/22/20.
[24]Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 7/22/20.
[25] 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.

pregnancy. Search terms included “REGN-EB3,” “atoltivimab,” maftivimab,” “odesivimag-ebgn,” OR “atoltivimab, maftivimab, and odesivimag-ebgn” AND “pregnancy,” “pregnant women,” “birth defects,” “congenital malformations,” “stillbirth,” “spontaneous abortion,” OR “miscarriage.” No relevant articles were identified.

LACTATION

Nonclinical Experience

Animal lactation studies have not been conducted with REGN-EB3.

Applicant’s Review of Published Literature

The applicant did not submit a literature review related to REGN-EB3 use during lactation.

DPMH’s Review of Published Literature

This Reviewer performed a search in *Medications and Mother’s Milk*[26], LactMed[27], Micromedex[22], Reprotox[24], Briggs[25], PubMed, and Embase to find relevant articles related to the use of REGN-EB3 during lactation. Search terms included “REGN-EB3, “atoltivimab,” maftivimab,” “odesivimag-ebgn,” OR “atoltivimab, maftivimab, and odesivimag-ebgn” AND “lactation” OR “breastfeeding.” No relevant articles were identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

(b) (4)

Applicant’s Review of Published Literature

The applicant did not submit a literature review related to REGN-EB3 effects on fertility.

DPMH’s Review of Published Literature

This Reviewer performed a search in PubMed, Embase, and Reprotox[24] to find relevant articles related to the use of REGN-EB3 and effects on fertility. Search terms included “REGN-EB3, “atoltivimab,” maftivimab,” “odesivimag-ebgn,” OR “atoltivimab, maftivimab, and odesivimag-ebgn” AND “fertility,” “contraception,” “oral contraceptives,” OR “infertility.” No relevant articles were identified.

DISCUSSION and CONCLUSIONS

Pregnancy

Overall, available data from the 16 pregnancies identified during the PALM RCT, PALM Extension, and EAP for REGN-EB3 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/neonatal morbidity and mortality observed in the PALM RCT and EAP are consistent with the published literature regarding the risks to pregnancy associated with underlying

[26] Hale, Thomas (2017) Medications and Mother’s Milk. Amarillo, Texas. Hale Publishing.

[27] 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 7/22/20.

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 *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 REGN-EB3 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 REGN-EB3 is a combination of 3 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 REGN-EB3 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 REGN-EB3. DPMH noted *Zaire ebolavirus* affects females of reproductive potential and the limited available human data on REGN-EB3 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 REGN-EB3, 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.

Lactation

There are no available data on the presence of REGN-EB3 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 REGN-EB3. 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 REGN-EB3.

Females and Males of Reproduction Potential

DPMH recommends omitting subsection 8.3 of REGN-EB3 labeling. There are no available human or animal studies evaluating the effect of REGN-EB3 on male or female fertility. Similarly, pregnancy testing and contraception subheadings are not applicable because there are no available data to suggest REGN-EB3 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 August 7, 2020. DPMH refers to the final BLA action for final labeling.

DPMH Proposed REGN-EB3 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 and an expanded access program in which pregnant women with *Zaire ebolavirus* infection were treated with TRADENAME 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 TRADENAME, are transported across the placenta (b) (4) therefore, TRADENAME has the potential to be transferred from the mother to the developing fetus. Animal reproduction studies have not been conducted with TRADENAME.

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 (b) (4) infected with *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 atoltivimab, maftivimab, and odesivimab 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 atoltivimab, maftivimab, or odesivimab 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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