CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761169Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761169
PDUFA Goal Date	October 25, 2020
OSE RCM #	2020-264
Reviewer Name(s)	Elizabeth Everhart, MSN, RN, ACNP
Team Leader	Naomi Boston, PharmD
Acting Deputy Division Director	Doris Auth, PharmD
Review Completion Date	August 10, 2020; date entered into DARRTS, August 20, 2020
Subject	Evaluation of Need for a REMS
Established Name	atoltivimab – odesivimab – maftivimab (REGN-EB3)
Trade Name	Inmazeb
Name of Applicant	Regeneron Pharmaceuticals, Inc.
Therapeutic Class	Human IgG monoclonal antibody
Formulation	Solution for infusion
Dosing Regimen	50 mg of each mAb/kg (3mL/kg) IV (b) (4) × 1

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity REGN3470-3471-3479 (atoltivimab, odesivimab, and maftivimab), also known as REGN-EB3, is necessary to ensure the benefits outweigh its risks. Regeneron Pharmaceuticals, Inc. submitted a Biologics Licensing Application BLA 761169 for REGN3470-3471-3479 with the proposed indication of treatment of adult and pediatric patients of infection caused by Zaire ebolavirus (EBOV). If approved, REGN-EB3 will be indicated as follows: 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. The serious risks associated with REGN-EB3 include hypersensitivity, including infusion-related (b) (4) as well as a recommendation to avoid concurrent administration with live vaccines. Neither of these risks will require a *Boxed Warning* in the product label. REGN-EB3 will likely be prescribed by healthcare practitioners who have experience in the use of medications to treat EBOV, including monoclonal antibodies and other drugs currently used in clinical trials and/or expanded access protocols. The applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of REGN3470-3471-3479 outweigh its risks. EBOV is a serious, life-threatening disease with a high case fatality rate and no approved therapy. While there has been some success in terms of prevention of EBOV with the approval of the Ervebo vaccine, there is still an unmet need for treatment of patients already infected. REGN-EB3 has an acceptable safety profile and was shown to have greater efficacy than the comparator product in the clinical trial with a decrease in mortality over comparator of 17% overall. This decrease in mortality is meaningful and clinically significant in a patient population with a life-threatening disease with currently no approved treatment.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) [a] REGN3470-3471-3479, referred to as REGN-EB3, is necessary to ensure the benefits outweigh its risks. Regeneron Pharmaceuticals, Inc. submitted a Biologic Licensing Application (BLA) 761169 for REGN-EB3 proposed for adult and pediatric patients for the treatment of infection caused by Zaire ebolavirus (EBOV). If approved, REGN-EB3 will be indicated as follows: 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. This application is under review in the Division of Antivirals (DAV). The applicant did not submit a proposed REMS or risk management plan with this application.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

2 Background

2.1 PRODUCT INFORMATION

REGN-EB3 is a combination of 3 human immunoglobulin G (IgG) monoclonal antibodies (mAbs) directed against different, non-overlapping epitopes on EBOV glycoprotein (GP). Each mAb, REGN3470 (atoltivimab), REGN3471 (odesivimab), and REGN3479 (maftivimab), is a human mAb (IgG1 isotype). It is supplied as a solution for infusion, proposed to be administered at a dose of 50 mg of each mAb/kg (3mL/kg) IV (b) (4) × 1.[b] REGN3470-3471-3479 is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761169 relevant to this review:

- 09/03/2019: Breakthrough designation granted
- 10/15/2019: Applicant informed at pre-NDA meeting that a REMS for REGN-EB3 was likely not needed
- 02/25/2020: BLA 761169 final submission for adult and pediatric patients for the treatment of infection caused by Zaire ebolavirus received
- 06/08/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for REGN-EB3

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Ebolavirus is a member of the *Filoviridae* family and is a single-stranded RNA virus, which includes genus Ebolavirus, as well as Marburgvirus and Cuevavirus; Ebolavirus and Marburgvirus are among the most virulent human pathogens[c], the Cuevavirus is only seen in bats. Ebolavirus consists of five subtypes: Zaire, Sudan, Tai Forest, Bundibugyo, and Reston[1]. The focus of this review will be the Zaire species of Ebolavirus. Zaire ebolavirus (EBOV) has caused many of the large outbreaks in Central Africa since it was first identified in 1976 and the outbreaks are at this time limited to Africa. It was the responsible agent in a 2014-2016 outbreak in West Africa and is also the causative agent in the current epidemic in the Democratic Republic of the Congo (DRC), ongoing since 2018. EBOV has a very high fatality rate of greater than 50% to close to 90% [d]. Most cases of Ebolavirus occur in Africa, with cases occurring as part

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

of periodic outbreaks. In the U.S., Ebolavirus is extremely rare and occurs only in cases where an individual infected in another country (usually Africa) travels to the U.S.[2]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Currently there are no FDA approved treatments for EBOV. Treatment is supportive, aimed at managing the symptoms of vomiting/diarrhea, fever, infection, and pain with intravenous medications, supplemental oxygen, fluid and electrolyte repletion, and other supportive measures which typically require hospitalization. A vaccine against EBOV, rVSV-ZEBOV (tradename Ervebo), found to be protective, was approved as a single vaccine regimen by the FDA in 2019 and is currently the only approved vaccine. As EBOV is quite contagious and has a high fatality rate and causes high morbidity and mortality in ongoing outbreaks, there is a clear unmet medical need to develop effective treatments to combat the disease.

4 Benefit Assessment

The efficacy and safety of REGN-EB3 for the treatment of EBOV in adult and pediatric patients was evaluated in the 19-I-003 PAmojaTuLinde Maisha (referred to as the PALM randomized controlled trial), phase 2/3 trial (NCT03719586). The PALM trial, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and the DRC INRB (Institut National de Recherche Biomedicale) is a multicenter, multi-outbreak, randomized, controlled, safety and efficacy study of investigational therapeutics for the treatment of patients with Ebola virus disease being conducted in four centers in the DRC. The study has four arms with patients randomized in a 1:1:1:1 fashion: ZMapp, a combination of three chimeric antibodies against EBOV GP; REGN-EB3; remdesivir, a small molecule antiviral drug; and a single neutralizing monoclonal antibody against EBOV GP, mAb114. ZMapp was chosen as the comparator arm for the other three products because, although ZMapp did not meet its prespecified efficacy endpoint in an earlier clinical trial due to the end of the 2014-2016 West African outbreak[3] , it did show a 40% relative risk reduction in mortality compared to optimized standard of care (oSOC) treatment[4].

For this NDA, the REGN-EB3 sponsor submitted data for patients enrolled comparing just ZMapp to REGN-EB3 as of August 9, 2019. The primary efficacy endpoint was 28-day mortality; REGN-EB3 was found to be superior to ZMapp in decreasing 28-day mortality, with a clinically significant 17.2% reduction over ZMapp and the data safety monitoring board recommended the PALM study be stopped early because REGN-EB3 was superior to ZMapp in preventing death based on pre-specified stopping criterion[e]. The clinical reviewer finds a superior benefit of REGN-EB3, combined with oSOC, in terms of improvement in 28-day mortality over ZMapp[5]. Table 1 shows a summary of the 28-day mortality results of ZMapp + oSOC compared to REGN-EB3 + oSOC, including results by baseline viral load. There is concern that the 52% difference in mortality in patients who received REGN-EB3 with high vs. a low viral load (referred to as CtNP, or Cycle threshold for nucleoprotein gene, in Table 1) might indicate that a

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

higher dose of REGN-EB3 might be needed for patients with high viral load[6]. At this time, discussions concerning possible PMR/C are ongoing but there is consideration for a PMR/C related to dose optimization.

Table 1 The Primary Efficacy Endpoint 28-Day mortality of PALM Trial by Baseline Viral Load (ITT Concurrent Population)[7]

Population / Subpopulation	Regn-EB3 (N=154) Death/Total (%)	ZMapp (N=153) Death/Total (%)	Rate Difference % (95% CI)[a]	Boschloo's 2-sided P-value[b]
ITT Concurrent	52/154 (33.8%)	78/153 (51.0%)	-17.2 (-28.0, -4.1)	0.0023
CtNP at Baseline				
CtNP ≤ 22	42/66 (63.6%)	56/64 (87.5%)	-23.9 (-38.5, -7.3)	0.0015
CtNP > 22	10/88 (11.4%)	22/88 (25.0%)	-13.6 (-25.3, -1.9)	0.0215

When the PALM trial initially began in November 2018, it included 3 treatment groups (ZMapp, remdesivir, and mAb114); in a protocol amendment of December 2018, the REGN-EB3 arm was added. The study found that mortality rates for REGN-EB3 and mAB114 were similar and so the DSMB recommended that the PALM RCT continue into an extension phase to randomize patients to either of those two arms to evaluate safety.

Additional supportive efficacy data from an expanded access protocol, EAP 1846, is also included in the NDA. EAP 1846 is an expanded access program that provided REGN-EB3 on a compassionate use basis to patients with EBOV and was begun concurrently with the PALM trial. The 28-day survival for patients who received REGN-EB3 of 68% in EAP 1846 was similar to that seen in the PALM trial (62%).

5 Risk Assessment & Safe-Use Conditions

The safety of REGN-EB3 was evaluated in 382 adults and pediatric patients with EBOV in one clinical trial and one expanded access program. Safety information was also supplemented from a first-in-human study (Study 1528) in 24 healthy subjects in which 18 patients received active treatment and 6 received placebo as a single dose; the most common treatment emergent adverse event (TEAE) was headache, followed by myalgia; there were no severe TEAEs and no deaths.

In the PALM trial, REGN-EB3 was evaluated in 154 patients (115 adults and 39 pediatric patients) and 168 received an investigational control in a randomized controlled trial conducted in 2018-2019 in the DRC during an EBOV outbreak, with both arms receiving optimized standard of care treatment. In the expanded access program during the same outbreak, REGN-EB3 was given to 228 patients (190 adults and 38 pediatric patients). The adverse event evaluations were confounded by similar signs and symptoms related to underlying EBOV infection. The following pre-specified symptoms, assessed on a daily basis, were reported in ≥ 40% of study subjects who received REGN-EBE: diarrhea (b) (4), pyrexia (b) (4) and vomiting (b) (4) with adverse event profiles similar between adult and pediatric subjects. Overall, the most commonly reported adverse events in at least 20% of subjects were pyrexia, chills, tachycardia, tachypnea, and vomiting. The safety database was comprised of results from the PALM trial as adverse events were not systematically collected in the EAP 1846 program[8].

At the time of this review, labeling negotiations are ongoing, but currently, as described in the sections below, labeling includes a *Warning and Precaution* for hypersensitivity, including infusion-related (b) (4) as well as a recommendation in the *Drug Interactions* section to avoid concurrent administration of live vaccines[f].

5.1 HYPERSENSITIVITY INCLUDING INFUSION-RELATED (b) (4)

If approved, labeling will advise in a *Warning and Precaution* that hypersensitivity reactions, including during and following infusion were reported in clinical trials with REGN-EB3. The reactions have the potential to be acute and life-threatening. The label further advises that patients should be monitored during and post-infusion for signs and symptoms of hypersensitivity, including (b) (4) hypotension, fever, and chills. In the clinical trials, the infusion of REGN-EB3 was stopped early due to an infusion-related reaction in 1% of patients. The label will advise that the rate of infusion should be slowed/interrupted if the patient develops any signs of an infusion-related reaction and the infusion stopped if a patient experiences a severe or life-threatening hypersensitivity reaction with appropriate emergency care instituted.

5.2 AVOIDING CONCURRENT ADMINISTRATION WITH LIVE VACCINES

If approved, the label will advise in the *Drug Interactions* section that no therapeutic-vaccine studies were performed in humans who received REGN-EB3. The label will further advise that there is the potential for REGN-EB3 to inhibit the efficacy of a live vaccine indicated for the prevention of EBOV, and so the concurrent use of a live vaccine during treatment with REGN-EB3 should be avoided. The label will recommend following current vaccination guidelines for information regarding the interval of time between a live vaccine and starting REGN-EB3.

6 Expected Postmarket Use

If approved, REGN-EB3 will likely be used in patients infected with EBOV in the inpatient hospital settings by infectious disease, primary care, or intensive care practitioners who will likely be experienced by their training with the use of medications to treat EBOV, including monoclonal antibodies and other drugs that are currently used in clinical trials and/or expanded access protocols.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for REGN-EB3 beyond routine pharmacovigilance and labeling.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of REGN-EB3 on the basis of the efficacy and safety information currently available. EBOV is a serious, life-threatening disease with a high case fatality rate and no approved treatment. While there has been some success in terms of prevention of EBOV with the approval of the Ervebo vaccine, there is still a clear need for treatment options for patients already infected. REGN-EB3 has an acceptable safety profile and was shown to have greater efficacy than the comparator product in the clinical trial with a decrease in mortality over comparator of 17% overall. This decrease in mortality is meaningful and clinically significant in a patient population with a life-threatening disease with no currently approved treatment options.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable, therefore, a REMS is not necessary for REGN-EB3 to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

[1] Bray, M, Chertow, D. Epidemiology and pathogenesis of Ebola virus disease. UpToDate, accessed June 8, 2020.

[2] CDC. Ebola Virus Disease, https://www.cdc.gov/vhf/ebola/prevention/index.html , accessed 7/23/20.

[3] Clinicaltrials.gov trial record for NCT03719586, accessed June 19, 2020.

[4] Regeneron. Clinical Overview for BLA 761169.

[5] FDA Integrated Review of BLA 761169, draft. Accessed 8/10/2020.

[6] Ibid, accessed 7/23/2020.

[7] Ibid, accessed 7/23/2020.

[8] Regeneron. Draft labeling for BLA 761169 as edited by FDA, accessed 7/10/2020 and 8/7/2020.

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/s/

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