CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761172Orig1s000

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	761172
PDUFA Goal Date	January 29, 2021
OSE RCM #	2020-1126, 2020-1127
Reviewer Name(s)	Brad Moriyama, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Acting Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	December 14, 2020
Subject	Evaluation of Need for a REMS
Established Name	ansuvimab-zykl
Trade Name	Ebanga
Name of Applicant	Ridgeback Biotherapeutics, LP
Therapeutic Class	*Zaire ebolavirus* glycoprotein (EBOV GP)-directed human monoclonal antibody
Formulation(s)	400 mg vial
Dosing Regimen	ansuvimab-zykl 50 mg/kg single intravenous infusion

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Ebanga (ansuvimab-zykl) is necessary to ensure the benefits outweigh its risks. Ridgeback Biotherapeutics, LP submitted a Biologic Licensing Application (BLA) 761172 for ansuvimab-zykl with the proposed indication 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 risk associated with ansuvimab-zykl include hypersensitivity reactions including infusion-associated events. The applicant did not submit a proposed REMS with this application but submitted a risk management plan.

DRM and the Division of Antivirals (DAV) agree that a REMS is not necessary to ensure the benefits of ansuvimab-zykl outweigh its risks. The efficacy of ansuvimab-zykl was supported by the PALM trial, in which the ansuvimab-zykl arm had a statistically significant and clinically meaningful survival benefit when compared to the active comparator ZMapp. The serious risk associated with ansuvimab-zykl of hypersensitivity reactions including infusion-associated events will be communicated in the warnings and precautions section of the label.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Ebanga (ansuvimab-zykl) is necessary to ensure the benefits outweigh its risks. Ridgeback Biotherapeutics, LP submitted a BLA 761172 for ansuvimab-zykl with the proposed indication 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.[1] This application is under review in the Division of Antivirals (DAV). The applicant did not submit a proposed REMS with this application but submitted a risk management plan.

2 Background

2.1 PRODUCT INFORMATION

Ebanga (ansuvimab-zykl), a NME, is a *Zaire ebolavirus* glycoprotein (EBOV GP)-directed human monoclonal antibody. Ansuvimab-zykl is proposed 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. It is supplied as a 400 mg vial for IV injection. The proposed dosing regimen is ansuvimab-zykl 50 mg/kg single intravenous infusion.[b] Ansuvimab-zykl was designated as an orphan product and breakthrough therapy. Ansuvimab-zykl is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

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

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

The following is a summary of the regulatory history for ansuvimab-zykl BLA 761172 relevant to this review:

- 05/08/2019: Orphan drug designation granted
- 09/06/2019: Breakthrough therapy designation granted
- 05/29/2020: BLA 761172 submission for 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 received
- 09/11/2020: 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 ansuvimab-zykl

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, the Cuevavirus is only seen in bats. Ebolavirus consists of five subtypes: Zaire, Sudan, Tai Forest, Bundibugyo, and Reston.[2,3] 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 was also the causative agent in the epidemic in the Democratic Republic of the Congo (DRC) from 2018-2020. EBOV has a very high fatality rate of greater than 50% to close to 90%.[c] Most cases of Ebolavirus occur in Africa, with cases occurring as part 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.[4,d]

3.2 Description of Current Treatment Options

Treatment of Ebolavirus disease includes supportive care, 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.[3,5] Recently, Inmazeb, a combination of *Zaire ebolavirus* glycoprotein-directed human monoclonal antibodies (atoltivimab, maftivimab, and odesivimab), was approved by the FDA in 2020 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.[6] The serious risk associated with

[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.*

Inmazeb include hypersensitivity reactions including infusion-associated events. Inmazeb does not have a boxed warning in its label or a REMS.

4 Benefit Assessment

The pivotal trial NCT 03719586 (PALM) supporting this application for efficacy and safety consisted of a Phase 2/3, multi-center, randomized, controlled trial which evaluated ansuvimab-zykl for the treatment of Ebolavirus disease.[1,7] Patients were enrolled in the North Kivu and Ituri provinces in the Democratic Republic of Congo during a *Zaire ebolavirus* outbreak. The PALM trial was designed as a master protocol and included four treatment arms including ZMapp (active investigational control arm), remdesivir, ansuvimab, and REGN-EB3.[7,8] The efficacy analysis for this application consisted of a comparison of ansuvimab-zykl and ZMapp. Patients were randomized to ansuvimab-zykl 50 mg/kg as a single intravenous infusion (N=174) or ZMapp (N=168). The primary efficacy endpoint was 28-day mortality. The PALM trial was stopped early on the basis of a pre-specified interim analysis showing a statistically significant reduction in mortality for ansuvimab-zykl compared to control. The ansuvimab-zykl group and ZMapp group had a 28-day mortality of 35% and 49%, respectively (mortality rate difference relative to control -14.3%, 95% CI -24.7 to -3.7, p=0.008). The FDA clinical reviewer concluded that the PALM trial indicated that in patients with Ebolavirus disease, the ansuvimab-zykl arm had a statistically significant and clinically meaningful survival benefit when compared to the active comparator ZMapp.[8,e]

5 Risk Assessment & Safe-Use Conditions

The safety of ansuvimab-zykl was evaluated in a Phase 2/3 clinical trial for the treatment of Ebolavirus disease (NCT 03719586, PALM).[1,8,f] In the safety population from PALM, 173 patients received ansuvimab-zykl and 168 patients received an investigational control (Zmapp). Two patients (1.1%) in the ansuvimab-zykl arm did not receive a complete infusion due to infusion-associated adverse events.[8] Common adverse reactions reported with ansuvimab-zykl included pyrexia, tachycardia, diarrhea, vomiting, hypotension, tachypnea, and chills.

The serious risk[g] associated with ansuvimab-zykl which include hypersensitivity reactions including infusion-associated events is summarized in the section below.

---

[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.*

[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.*

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

5.1 HYPERSENSITIVITY REACTIONS INCLUDING INFUSION-ASSOCIATED EVENTS

Hypersensitivity reactions including infusion-associated events, which may include acute, life-threatening reactions, have been reported with ansuvimab-zykl. The proposed label recommends monitoring for symptoms and signs of hypotension, chills and elevation of fever during and after ansuvimab-zykl infusion. It also recommends to discontinue ansuvimab-zykl immediately for severe or life-threatening hypersensitivity reactions and to administer appropriate emergency care. If approved, this risk will be communicated in the warnings and precautions section of the label.

6 Expected Postmarket Use

If approved, ansuvimab-zykl will primarily be used in inpatient settings. The likely prescribers will be critical care medicine practitioners and infectious diseases specialists.

7 Risk Management Activities Proposed by the Applicant

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

8 Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of ansuvimab-zykl on the basis of the efficacy and safety information currently available. The efficacy of ansuvimab-zykl was supported by the PALM trial, in which the ansuvimab-zykl arm had a statistically significant and clinically meaningful survival benefit when compared to the active comparator ZMapp. The serious risk associated with ansuvimab-zykl of hypersensitivity reactions including infusion-associated events will be communicated in the warnings and precautions section of the label.

Ebolavirus disease may be life threatening. Zaire ebolavirus has a very high fatality rate of greater than 50% to close to 90%. Most cases of Ebolavirus occur in Africa, with cases occurring as part of periodic outbreaks. In the U.S., Ebolavirus is extremely rare and occurs only in cases where an individual infected in another country travels to the U.S. Based on the PALM trial, ansuvimab-zykl offers an additional treatment option to patients with infection caused by *Zaire ebolavirus.* The likely prescribers will be critical care medicine practitioners and infectious diseases specialists who should have experience managing the serious adverse events reported with ansuvimab-zykl. If approved, based on the efficacy and risks associated with ansuvimab-zykl 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 DRM and DAV agree that a REMS is not necessary to ensure that the benefits outweigh the risks.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for ansuvimab-zykl 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] Proposed prescribing information for ansuvimab-zykl as currently edited by FDA, accessed November 16, 2020.

[2] Bray M, Chertow D. Epidemiology and pathogenesis of Ebola virus disease. UpToDate, accessed October 29, 2020.

[3] Everhart, E. Division of Risk Management NME review for atoltivimab – odesivimab – maftivimab (REGN-EB3), August 20, 2020.

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

[5] Feldmann H, Sprecher A, Geisbert TW. Ebola. N Engl J Med. 2020;382(19):1832-1842.

[6] Inmazeb (atoltivimab, maftivimab, and odesivimab-ebgn) package insert. Tarrytown, NY: Regeneron Pharmaceuticals Inc., 2020 October.

[7] Ridgeback Biotherapeutics, LP. Ansuvimab. Module 2.5. Clinical Overview. May 29, 2020.

[8] Ansuvimab-zykl BLA 761172 integrated review draft, accessed November 16, 2020.

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/

BRAD T MORIYAMA
12/14/2020 04:57:06 PM

NAOMI S BOSTON
12/15/2020 10:29:50 AM

DORIS A AUTH
12/16/2020 07:43:19 AM