CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761172Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	BLA
Application number(s)	761172
Priority or standard	Priority
Submit date(s)	5/29/2020
Received date(s)	5/29/2020
PDUFA goal date	1/29/2021
Division/office	Division of Antivirals (DAV)
Review completion date	12/21/2020
Established/proper name	Ansuvimab-zykl
(Proposed) proprietary name	Ebanga
Pharmacologic class	Zaire ebolavirus glycoprotein-directed monoclonal antibody
Code name	Ansuvimab-zykl (mAb114; VRCEBOMAB092-00-AB)
Applicant	Ridgeback Biotherapeutics, LP
Dosage form(s)/formulation(s)	Solution for injection
Dosing regimen	The recommended dosage of Ebanga is 50 mg/kg diluted and administered as a single intravenous infusion administered over 60 minutes
Applicant proposed indication(s)/ population(s)	Treatment of infection caused by Zaire ebolavirus
Proposed SNOMED indication	37109004 | Ebola virus disease (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	For injection: 400 mg of ansuvimab-zykl, available as an off-white to white lyophilized powder in single-dose vial for reconstitution and further dilution.
Approved indication(s)/ population(s) (if applicable)	EBANGA 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. Limitations of Use The efficacy of EBANGA has not been established for other species of the Ebolavirus and Marburgvirus genera. Zaire ebolavirus can change over time, and factors such as emergence of resistance, or changes in viral virulence could diminish the clinical benefit of antiviral drugs. Consider available information on drug susceptibility patterns for circulating Zaire ebolavirus strains when deciding whether to use EBANGA
Approved SNOMED term for indication (if applicable)	37109004 | Ebola virus disease (disorder)

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Glossary

AE	adverse event
ADCC	antibody-dependent cellular cytotoxicity
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLA	biologics license application
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
cITT	concurrent intent-to-treat
C_{max}	maximum plasma concentration
CRF	case report form
CSF	cerebral spinal fluid
DAV	Division of Antivirals
DRC	Democratic Republic of the Congo
DSMB	data safety monitoring board
EAP	expanded access program
EBOV	*Zaire ebolavirus*
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ETU	Ebola treatment unit
FDA	Food and Drug Administration
GE	genome equivalent
GLP	good laboratory practice
GP	glycoprotein
IC_{50}	half maximal inhibitory concentration
ICH	International Council on Harmonisation
IM	intramuscular
IND	investigational new drug
INRB	Institut National de Recherche Biomédicale
ITT	intent-to-treat
IV	intravenous
KM	Kaplan-Meier
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MLD	mucin-like domain
NDA	new drug application
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institute of Health
oITT	overall intent-to-treat
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigations
oSOC	optimized Standard of Care
PALM	PAmoja TuLinde Maisha

PEP	postexposure prophylaxis
PK	pharmacokinetic
PLLR	Pregnancy and Lactation Labeling Rule
PMC	postmarketing commitment
PMR	postmarketing requirement
PST	protocol study team
RBD	receptor binding domain
RCT	randomized, controlled trial
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SOP	standard operating procedure
SUSAR	serious, unexpected, and suspected adverse reaction
UNMC	University of Nebraska Medical Center
USAMRIID	United States Army Medical Research Institute of Infectious Diseases
VRC	Vaccine Research Center
WHO	World Health Organization

I. Executive Summary

1. Summary of Regulatory Action

This new biologics license application (BLA) for Ebanga™, a human recombinant IgG1 monoclonal antibody (mAb) targeted against the glycan cap and core domains in the GP1 subunit of the *Zaire ebolavirus* (EBOV) glycoprotein, was submitted by Ridgeback Biotherapeutics, LP. The BLA was reviewed by a multidisciplinary team. The intended indication is for the treatment of infection caused by EBOV in adult and pediatric patients, including neonates born to a mother who is positive by reverse transcriptase-polymerase chain reaction for EBOV infection. Ebanga (initially named mAb114 but subsequently named ansuvimab-zykl and will be referred to as ansuvimab-zykl throughout the review) is only the second product to be approved for the treatment of EBOV infection.

The regulatory history is notable for Orphan Drug designation and Breakthrough Therapy designation. This BLA received a Priority Review and was not presented at the Antimicrobial Drugs Advisory Committee, because ansuvimab-zykl received Breakthrough Therapy designation, and the benefit-risk assessment was not controversial based on the review team's preliminary assessment of the trial results.

No discipline (Clinical, Clinical Virology, Clinical Pharmacology, Pharmacology/Toxicology, Statistics and Regulatory) identified issues precluding approval. I, the signatory authority, agree that the benefit-risk assessment favors approval.

Originally, the development program for ansuvimab-zykl was based on fulfilling the necessary criteria for potential approval under the Animal Rule pathway. However, when a new outbreak of EBOV infection was declared in the Democratic Republic of the Congo (DRC) in 2018, an expanded access protocol for emergency use was implemented followed by the initiation of the PAmoja TuLinde Maisha (PALM) trial by the National Institute of Allergy and Infectious Diseases (NIAID) and the Institut National de Recherche Biomédicale (INRB) of the DRC with support from other donors. The nonhuman primate challenge studies in rhesus macaques along with the Phase 1 data in healthy volunteers provided the basis to evaluate a single dose of 50 mg/kg ansuvimab-zykl in the PALM Trial.

The PALM Trial compared three investigational agents (two mAb products and one small molecule) to an investigational control ZMapp (another mAb). The use of ZMapp as the investigational control arm was deemed acceptable by the review team based on the results from the PREVAIL II trial, local health authority preference, and the superiority trial design (review issue discussed in Section 6.3.1).

The results of the PALM Trial clearly demonstrated efficacy to support the approval of ansuvimab-zykl for the treatment of adult and pediatric patients infected with EBOV. The PALM Trial was stopped early on the basis of a prespecified interim analysis and showed a significant reduction in mortality for ansuvimab-zykl (35%) compared to control (49%). The results from this single trial are adequate to support approval because of the significant results. However,

lower efficacy was seen in subjects with a cycle-threshold nucleoprotein gene target value of ≤22 (CtNP <22; which correlates with a higher viral load) versus those with a value of >22. Although the PALM Trial demonstrated ansuvimab-zykl was efficacious, some uncertainties remain, including whether a higher dose of the mAb is needed for an optimally efficacious dose in patients with high baseline viral loads (review issue discussed in Section 6.3.2). A postmarketing commitment was issued to evaluate the efficacy, safety, and pharmacokinetics of a higher dose of ansuvimab-zykl versus ansuvimab-zykl 50 mg/kg in adult and pediatric patients with CtNP gene target values of ≤22.

Based on the data submitted, ansuvimab-zykl has a favorable safety profile. Although some clinical assessments were limited by the challenging circumstances at the study sites, the safety database is sufficient for the evaluation of risk. Having met the primary efficacy objective, superiority in reduction of 28-day mortality, a degree of uncertainty in describing the risk attributable to ansuvimab-zykl was considered acceptable. Infusion-associated events, such as hypotension, chills, and elevation of fever, were reported peri- and postinfusion. The WARNINGS AND PRECAUTIONS section included a description of the potential for hypersensitivity reactions and recommendations for monitoring and mitigation of infusion-related reactions. The evaluation of adverse events (AEs) in subjects who received ansuvimab-zykl may have been confounded by the signs and symptoms of the underlying EBOV infection. The most common AEs reported in at least 5% of subjects were pyrexia (or elevation in fever), chills, tachycardia, diarrhea, vomiting, hypotension, and tachypnea. Overall, the AE profile in adult and pediatric subjects treated with ansuvimab-zykl was similar.

The resistance pathway for ansuvimab-zykl was not characterized and no human resistance data were available from the PALM Trial. Two postmarketing requirements were issued to characterize the resistance profile.

One review issue related to the evaluation of benefit is the lack of clinical data for the treatment of EBOV infection acquired by routes other than natural transmission. The PALM Trial and the expanded access protocol treated subjects presumably infected by the natural transmission route (i.e., contact with infected blood or other bodily fluid). The nonclinical studies did not model other routes of infection, such as an intentional release of virus via aerosol or a needlestick exposure. The Clinical Virology team's position is that the indication should state naturally-acquired infection given that a needlestick exposure, which may involve a markedly greater inoculum, was not studied and the disease course is likely to be significantly different in the event of an intentional release. The Clinical review team agreed that the nonhuman primate studies were inadequate to demonstrate evidence of efficacy in the setting of needlestick injuries or intentional release; however, restricting its use to naturally-acquired infection could result in delay or deferral of therapy in these circumstances despite the demonstrated robust mortality benefit observed in naturally occurring infection and the potential for benefit in the context of needlestick exposure or other healthcare-associated exposures. The signatory concurs with the Clinical review team. Therefore, the indication does not reference route of infection and remains treatment of infection caused by EBOV.

Based upon review of all available efficacy and safety data, the benefits of ansuvimab-zykl clearly outweigh the risks for treatment of EBOV. The availability of ansuvimab-zykl will provide an effective treatment option for adult and pediatric patients, including neonates and pregnant individuals, infected with EBOV.

For detailed information supporting the basis for the benefit-risk assessment please refer to the details in this integrated assessment document.

2. Benefit–Risk Assessment

2.1. Benefit–Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• *Ebolavirus* is a large, nonsegmented, negative-sense, single-stranded RNA virus that is the causative agent of Ebolavirus disease, formerly known as Ebola hemorrhagic fever in humans. *Ebolavirus* been associated with large outbreaks in Africa over the last 40 years (Centers for Disease Control and Prevention 2020c) • *Zaire ebolavirus* (EBOV) is one of four filoviruses that are highly pathogenic and can cause severe systemic and potentially fatal disease in humans and nonhuman primates (NHPs) (Centers for Disease Control and Prevention 2020b) • Since 1976, there have been multiple Ebola outbreaks with cases detected in many countries and fatality rates of approximately 50%. Mortality rates vary by outbreak, treatment setting, and availability of optimized supportive care and have ranged from 25% to 90% (Centers for Disease Control and Prevention 2020a; World Health Organization 2020) • Until 2013, Ebolavirus outbreaks had been confined to subSaharan Africa, mainly in central African countries including Gabon, Republic of Congo, the Democratic Republic of the Congo (DRC), Sudan, and Uganda. • More recently, starting with the 2013 to 2014 West Africa *Zaire ebolavirus* outbreak, several countries reported imported *Zaire ebolavirus* cases, including 11 reported cases in the US. Given the frequency of international travel, *Zaire ebolavirus* infection remains a global threat to public health.	Direct contact with bodily fluids contaminated with *Zaire ebolavirus* causes a highly contagious infection that results in ebolavirus disease, a rapidly progressive and often fatal infection. While outbreaks have predominantly occurred in western and equatorial Africa, it spread internationally in the 2014 to 2016 oubreak in West Africa and caused considerable alarm worldwide. Control of this disease has required extensive international collaboration with expansive mobilization of resources to detect and respond to outbreaks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• *Zaire ebolavirus* infection has an incubation period of 2 to 21 days followed by a rapid onset of nonspecific symptoms, such as high fever, fatigue, malaise, and body aches (Malvy et al. 2019)	
Current Treatment Options	• Currently there is one FDA-approved therapy for the treatment of *Zaire ebolavirus* infection. On October 14, 2020, FDA approved Inmazeb (atoltivimab, maftivimab, and odesivimab-ebgn), a mixture of three monoclonal antibodies, as the first FDA-approved treatment for *Zaire ebolavirus* infection in adult and pediatric patients. Data to support the approval for Inmazeb were also from the PALM Trial (19-I-0003). • A recombinant vesicular stomatitis virus (rVSV-ZEBOV) vaccine (tradename "Ervebo") was approved for prevention of EBOV infection on December 19, 2019. Ervebo is a single dose vaccine regimen that was found to be safe and protective against only the *Zaire ebolavirus* species of *Ebolavirus*. This was the first FDA approval of a vaccine for EBOV. • The standard of care remains supportive management . This includes oral and intravenous fluids, electrolyte replacement, maintaining oxygen status and blood pressure, and managing fever and pain. If subjects are also positive for malaria, antimalarial treatment is recommended. Antibiotics are recommended for severely ill patients given the risk of bacterial sepsis. Fresh whole blood, red blood cells, or fresh frozen plasma may also be used in instances of acute significant bleeding (World Health Organization 2020)	There is one recently FDA-approved therapy for the treatment of *Zaire ebolavirus* infection; data to support the approval of Inmazeb were also from the PALM Trial. While a vaccine has been approved for the prevention of *Zaire ebolavirus* infection, it cannot treat existing infections. The availability of another effective, well-tolerated therapy that can be used for patients of any age is highly desirable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Evidence for the effectiveness of ansuvimab-zykl to treat *Zaire ebolavirus* infection was established in a Phase 2/3 randomized controlled trial (RCT) conducted in a *Zaire ebolavirus* outbreak in the DRC (Study NIH-19-I-0003). Based on survival data assessing four investigational therapies evaluated in this study, two therapies emerged as lead therapeutic candidates, one of which was ansuvimab-zykl. • In this trial, subjects ranging in age from 1 day to 85 years old received treatment with 50 mg/kg dose of ansuvimab-zykl. Treatment with ansuvimab-zykl resulted in a clinically meaningful and statistically significant survival benefit compared to the active comparator, ZMapp, at Day 28 (mortality 35.1% versus 49.4%, respectively; p=0.008). • Additional supportive data from a noncontrolled study, the MEURI Expanded Access Program (EAP) in subjects 6 days to 80 years old, demonstrated a similar mortality rate as the NIH-19-I-0003 RCT. In the MEURI EAP, the mortality rate in patients treated with ansuvimab-zykl was 32.3% at 21 days; comparable to the mortality rate reported at 28 days in the pivotal RCT. • Ansuvimab-zykl-treated subjects with a low baseline viral load (CtNP >22) had a lower 28-day mortality rate (9.9%) compared to ansuvimab-zykl-treated subjects with a high viral load (CtNP ≤22; mortality rate 69.9%). A similar impact on mortality related to low and high baseline viral load was demonstrated in ZMapp-treated subjects, though the mortality rate was higher in both groups (23.7% and 85.7%, respectively). Similar findings for ansuvimab-zykl were noted in the MEURI EAP study with mortality rates of 15.3% and 63.6%, for low and high viral loads, respectively. Intrinsic and extrinsic factors, such as age, sex, Ebola treatment center, Ebola vaccination status, and median time to discharge, had no effect on the efficacy of ansuvimab-zykl, demonstrating consistency of the efficacy findings.	Subjects treated with ansuvimab-zykl had a significantly lower mortality rate compared to the active comparator (that was not affected by underlying intrinsic and extrinsic factors), thereby demonstrating the robustness of the findings. The comparability of mortality outcomes in the noncontrolled Expanded Access Program and Study NIH-19-I-0003 provides further reassurance of the treatment effect of ansuvimab-zykl in *Zaire ebolavirus* infection. The consistently lower mortality rate in subjects with a lower baseline viral load (>22 CtNP) confirms the importance of viral load on outcomes.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Safety was determined in a Phase 1 healthy human subjects study (NIH-18-I-0069) conducted in the United States, and in the Phase 2/3 pivotal RCT (NIH-19-I-0003) conducted during the 2018 *Zaire ebolavirus* outbreak in the DRC. • In the first trial conducted in healthy subjects, the ansuvimab-zykl infusion was well-tolerated and there were no local infusion-site reactions reported. All adverse events (AE) reported were solicited systemic reactogenicity-related events and were mild; none led to study withdrawal. • In the RCT study (NIH-19-I-0003): o The incidence of serious adverse events (SAE) was low and similar between ansuvimab-zykl (6%) and the active comparator, ZMapp (4%). None of the SAEs were related to ansuvimab-zykl. o The incidence of solicited infusion-related AEs was substantially lower in the ansuvimab-zykl arm compared to the comparator arm, and only 2 subjects (1%) in the ansuvimab-zykl arm had to discontinue the infusion compared to 13 (8%) in the ZMapp comparator arm. o Daily AEs assessed postinfusion were relatively similar between arms and could not be distinctly separated from the underlying *Zaire ebolavirus* infection. o There was no difference between the two arms regarding changes in vital signs or clinical laboratory values. o During the study, five pregnant women were enrolled into the ansuvimab-zykl arm and four into the ZMapp arm. All women survived but all had miscarriages except for one infant in the ZMapp arm who had birth defects.	The side-effects observed with ansuvimab-zykl infusion were mild and self-limited and were substantially lower than those seen in the comparator arm. Side-effects reported on follow-up days after the infusion were similar between both arms and could not be differentiated from the underlying *Zaire ebolavirus* infection.

2.2. Conclusions Regarding Benefit-Risk

The safety and efficacy data submitted in this BLA support the approval of ansuvimab-zykl (Ebanga) for the treatment of ebolavirus disease caused by *Zaire ebolavirus* infection, irrespective of age. During an outbreak in the DRC in 2018, ansuvimab-zykl was evaluated in a multicenter, randomized controlled trial (RCT) where survival data were assessed for four investigational therapies (one of which was an active comparator). In this study, treatment of *Zaire ebolavirus* infection with a single 50 mg/kg dose of ansuvimab-zykl resulted in a clinically meaningful and statistically significantly lower mortality compared to the active comparator, ZMapp, at Day 28 (35.1% versus 49.4%, respectively; p=0.008). Additional supportive data from a noncontrolled study, the MEURI Expanded Access Program, demonstrated that the mortality rate (32.3% at 21 days) in patients receiving ansuvimab-zykl was comparable to the mortality rate demonstrated in the RCT, and much lower than the overall mortality rate of 66% recorded in this outbreak . Intrinsic and extrinsic factors, such as age, sex, Ebola treatment center, Ebola vaccination status, and median time to discharge, had no effect on the efficacy of ansuvimab-zykl, demonstrating consistency of the efficacy profile. The impact of the viral load (CtNP category) on mortality rates confirm the importance of viral load at time of treatment initiation in treatment outcomes, where subjects with lower viral loads (CtNP >22) had statistically significantly lower mortality rates compared to those with higher viral loads.

Ansuvimab-zykl was found to be safe and well-tolerated in a Phase 1 study of healthy subjects. Adverse events associated with infusion in the pivotal Phase 2/3 RCT study in *Zaire ebolavirus* infected patients in the DRC occurred less frequently in the ansuvimab-zykl arm compared to the comparator arm, and only two subjects (1%) in the ansuvimab-zykl arm had to discontinue the infusion. There were few serious AEs (6%), and none of them were related to ansuvimab-zykl. There was no difference between the two arms regarding changes in vital signs, clinical laboratory values, or pregnancy outcomes.

In conclusion, the benefit of ansuvimab-zykl for the treatment *Zaire ebolavirus* infection outweighs its risks, and we recommend approval of ansuvimab-zykl for the treatment of ebolavirus disease due to *Zaire ebolavirus* infection in patients irrespective of age, including pregnant women.

II. Interdisciplinary Assessment

3. Introduction

The Applicant submitted this BLA for Ebanga (ansuvimab-zykl), also known as mAb114, a human immunoglobulin G (IgG) monoclonal antibody (mAb) directed against *Zaire ebolavirus* (EBOV) glycoprotein (GP). The requested indication is for the treatment of infection caused by EBOV in adult and pediatric patients. Ansuvimab-zykl has not been evaluated against other species of the *Ebolavirus or Marburgvirus* genera.

There is only one recently approved treatment for EBOV infection, Inmazeb™ (atoltivimab, maftivimab and odesivimab-ebgn), also known as REGN-EB3, which is a combination of three human IgG mAbs directed against *Zaire ebolavirus* glycoproteins. Given the high fatality rates and resulting disruption that occurs with EBOV outbreaks, more than one safe and effective treatment is highly desirable.

Due to the challenges and limitations associated with studying EBOV infection in the clinical setting, the initial ansuvimab-zykl development program was based on fulfilling the criteria for approval under the Animal Rule. An initial Phase 1 dose-escalation study in 18 healthy adult subjects conducted by the National Institute of Health (NIH) Clinical Center indicated the drug was safe and well-tolerated and had a pharmacokinetic (PK) profile consistent with that of other IgG1 mAbs. Nonhuman primate challenge studies provided initial proof-of-concept and informed the choice of dose used in the first treatment studies in EBOV-infected subjects. In collaboration with the World Health Organization (WHO), ansuvimab-zykl was provided for the emergency response during the 2018 to 2020 outbreak in North Kivu and Ituri provinces in the Democratic Republic of the Congo (DRC). Starting on November 20, 2018, with extraordinary international and interagency coordination between the US NIAID, the DRC Institut National de Recherche Biomédicale and humanitarian nongovernmental organizations (NGOs), the PAmoja TuLinde Maisha (PALM) trial was initiated at four sites. PALM was a multicenter, open-label, randomized controlled superiority trial (RCT) of four therapeutic candidates, including ansuvimab-zykl. On August 9, 2019, because a superiority finding for ansuvimab-zykl and REGN-EB3 over the active investigational control arm (ZMapp) was demonstrated, the data safety monitoring board (DSMB) recommended stopping PALM before the planned enrollment was complete. PALM was continued with an Extension Phase, where subjects were randomized to either ansuvimab-zykl or REGN-EB3.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

The review team identified five review issues relevant to the evaluation of benefit (Section 6.3):

- Use of an investigational drug, ZMapp, as an active control instead of optimized standard of care (oSOC) alone.
- Lower efficacy in ansuvimab-zykl-treated subjects with high viral loads (baseline CtNP values ≤22) versus subjects with low baseline viral loads (CtNP >22).
- Adequacy of clinical experience with pediatric subjects.
- Lack of clinical experience with ansuvimab-zykl for treatment of EBOV infection acquired by routes other than natural transmission.
- Use of an inadequately validated bioanalytical assay to measure concentrations of ansuvimab-zykl in the serum of healthy humans raised concerns about the reliability of the resulting PK data.

3.1.2. Key Review Issues Relevant to Evaluation of Risk

The review team also identified three review issues relevant to the evaluation of risk and risk management (Section 7.7):

- Risks associated with endotoxin levels for the proposed total infusion volumes and infusion times for pediatrics, and administration issues in neonates.
- The development of resistance against ansuvimab-zykl has not been adequately characterized.
- Potential risks of immunogenicity.

3.2. Approach to the Review

Table 3 provides an overview of the clinical trials to support the benefit and risk assessment for ansuvimab-zykl. The PALM Trial (NCT03719586, protocol number 19-I-0003) was the primary source of evidence to support the finding of efficacy. The review of clinical safety considered all available clinical experience in the context of the challenges inherent with EBOV outbreaks and the sociopolitical challenges occurring in the location of the outbreak. Because mortality was the primary efficacy endpoint of the PALM RCT, the ascertainment of benefit and the determination of safety may overlap in the setting of an indication with high morbidity and mortality. With the demonstration of a statistically significant treatment effect on mortality, especially with consistent findings for key secondary efficacy endpoints, a degree of uncertainty with the assessment of safety was acceptable.

Some of these uncertainties that could not be addressed were due to the limited clinical follow-up during the PALM Trial and MEURI expanded access program (EAP) study, including whether ansuvimab-zykl had any impact on long-term outcomes, such as late recurrence due to persistence in immune-privileged sites. Additionally, no formal vaccine interaction studies were performed (see additional discussion in Section 8.2). Of particular concern is whether ansuvimab-zykl may inhibit replication of a live virus vaccine indicated for prevention of EBOV infection and possibly reduce the efficacy of the vaccine.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Ebanga (Ansuvimab-zykl)

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
NIH 18-I-0069	Male and female healthy adults ages 18-60	Phase 1 open-label, dose escalation study Control type: None Randomization: None Blinding: None Biomarkers: PK of ansuvimab-zykl ADA to ansuvimab-zykl	Ansuvimab-zykl Single dose: 5, 25, or 50 mg/kg by intravenous infusion	Primary: To evaluate the safety and tolerability of a single dose of ansuvimab-zykl in healthy adults. Secondary: - To evaluate PK of ansuvimab-zykl at each dose level at representative timepoints - To determine whether ADA to ansuvimab-zykl can be detected in recipients of ansuvimab-zykl	18 subjects 5 mg/kg, n=3; 25 mg/kg, n=5; 50 mg/kg, n=10	One center in the United States: NIH Clinical Center Vaccine Evaluation Clinic, Bethesda, Maryland.

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
19-I-0003 (PALM Trial) (NCT03719586)	Persons with confirmed EBOV infection at a participating ETU	Control type: Active control (ZMapp) Randomization: Randomized Blinding: Open-label Biomarkers: RT-PCR viral load over time	• ZMapp, 50 mg/kg IV q3d x 3 doses, or • REGN-EB3, 150 mg/kg IV x 1 dose, or • Ansuvimab-zykl, 50 mg/kg IV x 1 dose, or • Remdesivir, IV with a 200 mg loading dose (5 mg/kg for pediatric subjects ≤40 kg) on day 1 followed by 9 to 13 days of once-daily maintenance dosing starting on day 2 and extending through days 10 to 14 Number treated. (Number randomized): Ansuvimab-zykl: 174 (176 randomized) ZMapp: 168 (169 randomized)	Primary: 28-day mortality Secondary: • Safety and tolerability. • Mortality rates for subjects with high viral load (CtNP ≤22) versus low viral load (CtNP >22). • Time to discharge from ETU. • Time to death. • Time to first negative Ebola virus rt-PCR results. • Time to two consecutive negative Ebola virus rt-PCR results.	Total of 500 subjects initially planned, amended to 725. Actual total enrollment: 681 randomized	Four centers (Beni, Butembo, Katwa, and Mangina), each in 1 country (DRC)

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
VRC Ansuvimab-zykl EAP (MEURI EAP)	Patients with confirmed EBOV infection presenting at an ETU in the DRC.	Control type: No control Randomization: No randomization Blinding: No blinding	Ansuvimab-zykl, 50 mg/kg IV x 1 dose. Number treated: 251 subjects	Primary: • To treat patients with Zaire ebolavirus infection • Treat subjects with a high-risk exposure to EBOV as postexposure prophylaxis Secondary: • Collect basic outcomes data including hypersensitivity reactions, self-reported adverse events and survival data	No specific number of individual subjects were planned	Seven sites, in 1 country (DRC)

Source: Reviewer
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled"
Abbreviations: BID, twice daily; DB, double-blind; LTE, long-term extension study; MC, multicenter; N, number of subjects; OL, open-label; PC, placebo-controlled; PG, parallel group; R, randomized

4. Patient Experience Data

Due to the limitations and challenges of conducting a trial for acute EBOV infection (particularly with the social-political environment in the DRC, patient experience data were not collected in the PALM Trial. However, for future consideration and to assess long-term outcomes, survivor studies may benefit from the collection of patient experience data. The sequelae of EBOV infection can include arthralgia, myalgia, headache, neuropsychiatric, testicular, and ophthalmic disorders. Survivors of previous outbreaks have also reported varying degrees of functional impairment (Qureshi et al. 2015). It is unclear whether early intervention with treatments such as ansuvimab-zykl can mitigate these sequalae.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	Not Applicable
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	Not Applicable
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	Not Applicable
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

The PK of ansuvimab-zykl was only evaluated in healthy human volunteers. The protocol for the PALM Trial allowed for PK sample collection where sample processing could be performed safely, and serial samples stored appropriately. However, no PK data were reported for subjects in the PALM Trial nor the MEURI EAP due to challenges associated with the safe transport of EBOV-infected serum samples from the study site to the designated site for PK analysis (outside of the DRC).

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Ansuvimab-zykl is a *Zaire ebolavirus* glycoprotein-directed monoclonal antibody
Mechanism of action	Ansuvimab-zykl is a recombinant human IgG1 monoclonal antibody that inhibits *Zaire ebolavirus*.
Active moieties	The active moiety is ansuvimab-zykl
QT prolongation	Monoclonal antibodies have a low likelihood of causing QT prolongation. Thus, the effect of ansuvimab-zykl on QT interval was not evaluated.
	General Information
Bioanalysis	An ELISA assay was used to quantify ansuvimab-zykl concentrations in serum obtained from uninfected humans. Because the assay was inadequately validated, the reliability of the PK data described below is unknown. (b) (4) Subsection 12.3 of the labeling (b) (4) a qualitative statement noting the general similarity of ansuvimab-zykl's PK profile to that of other IgG1 mAbs.
Healthy subjects versus patients	PK data are available in uninfected healthy adults, but not in Ebola-infected patients
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	Following a single IV dose of 50 mg/kg in healthy adults, mean ansuvimab-zykl exposures expressed as mean ± SD were as follows: $AUC_{0\text{-last}}$: 29288.3 day·µg/mL ±6168.6 C_{max}: 1932.3 µg/mL ±301.5
Range of effective dosage(s) or exposure/ maximally tolerated dosage or exposure	Both the PALM Trial and MEURI EAP evaluated a single dose of 50 mg/kg; no ansuvimab-zykl exposures were measured in these studies.
Dosage proportionality	At doses of 5 mg/kg to 50 mg/kg, C_{max} was dose-proportional but $AUC_{0\text{-last}}$ increased slightly more than dose-proportionally
Bridge between to-be-marketed and clinical trial formulations	Both the to-be-marketed lyophilized product and a liquid frozen product were used in clinical studies. The Applicant conducted an analytical comparability assessment to demonstrate comparable quality attributes of the two products (see the OBP Product Quality Review by Dr. Davinna Ligons uploaded to Panorama on 12/16/2020).

Characteristic	Drug Information
	Absorption
T_{max}	Mean T_{max} was 2.3 h following a 30 min infusion of a 50 mg/kg dose in healthy adults
	Distribution
Volume of distribution	In healthy adults, the ansuvimab-zykl volume of distribution was 74.5 mL/kg
	Elimination
Mass balance results	Not applicable
Clearance	In healthy adults, the clearance of ansuvimab-zykl was 1.66 mL/day/kg
Half-life	In healthy adults, the half-life of ansuvimab-zykl was 31.6 days
	Intrinsic Factors and Specific Populations
Body weight/age	Because PK was only evaluated in healthy adults aged 22-56 years with a body mass index within the normal range, the impact of age (either pediatric or geriatric) or obesity on PK has not be evaluated.
	Immunogenicity (for Biologics)
Bioanalysis	A sub-optimally validated nonquantitative, titer-based immunoassay was used to detect anti-ansuvimab-zykl antibodies in healthy human serum samples (see the OBP Immunogenicity Review by Dr. Davinna Ligons uploaded to Panorama on 12/16/2020). Consequently, the reliability of the resulting immunogenicity data is unknown.
Incidence	Two baseline serum samples were positive for anti-ansuvimab-zykl antibodies. However, a confirmatory assay was not conducted to support these findings. All samples were negative for anti-ansuvimab-zykl antibodies at Days 28 and Day 56.
Clinical impact	Given the concerns associated with the reliability of the immunogenicity data from Study 18-I-0069, (b) (4) Subsection 6.2 of the labeling. Instead, a general statement acknowledging the potential for immunogenicity with ansuvimab-zykl is provided. In healthy volunteers, the detection of anti-ansuvimab-zykl antibodies at baseline did not appear to impact PK or safety. The incidence or implications of anti-ansuvimab-zykl antibodies in EBOV-infected patients has not been evaluated.

5.1. Nonclinical Assessment of Potential Effectiveness

The nonclinical data support the potential effectiveness of ansuvimab-zykl based on the following findings (see Section 18 for detailed reviews of these study reports).

Mechanism of Action

- A summary of the data supporting the ansuvimab-zykl mechanism of action is provided in Table 6.
- Ansuvimab-zykl is a recombinant, fully human, gamma immunoglobulin type 1 kappa (IgG1κ) mAb that targets the *Zaire ebolavirus* glycoprotein, preventing EBOV entry into cells.
- Ansuvimab-zykl was derived from a monoclonal antibody isolated from the peripheral blood mononuclear cells of a subject who both survived the 1995 Ebolavirus outbreak in Kikwit, DRC and maintained circulating antibody for more than 10 years after infection.
- The EBOV GP epitope targeted by ansuvimab-zykl is linear and comprised of GP amino acid residues 111-LEIKKPDGS-119.
- Ansuvimab-zykl binds EBOV GP without the mucin domain with a K_D of 0.2nM at pH 7.4 and 0.6nM at pH 5.3 as measured by biolayer interferometry.
- Ansuvimab-zykl blocks binding of EBOV GP1 to the Neiman Pick cell receptor 1 (NPC1) on host cells, inhibiting virus entry into the host cell.
- Binding of ansuvimab-zykl to GP blocks interaction between GP and NPC1.
- Ansuvimab-zykl exhibited Fc-mediated antibody-dependent cellular cytotoxicity (ADCC) activity against cells expressing EBOV GP when effector cells were added.

Table 6. Summary of Ansuvimab-zykl Mechanism of Action Studies

mAb	Binds sGP	Binds GP	GP Binding (ELISA; µg/mL)	K_D (BLI; nM)	Blocking	Epitope Type	Binding Region	Epitope
Ansuvimab-zykl	Yes	Yes	0.02	0.2nM at pH 7.4 0.6nM at pH 5.3	Binding of ansuvimab-zykl to GP blocks interaction between GP and NPC1	Linear	Glycan cap and inner chalice of the EBOV GP1 subunit	111-119: LEIKKPDGS

Source: Review team analysis
Abbreviations: BLI, biolayer interferometry; EBOV, *Zaire ebolavirus*; ELISA, enzyme-linked immunosorbent assay; GP, glycoprotein; sGP, secreted glycoprotein

Cell Culture Antiviral Activity

- Ansuvimab-zykl neutralized lentiviral particles pseudotyped with EBOV GP (Mayinga variant) in HEK293 cells with an EC_{50} value of 0.09 µg/mL.

- Ansuvimab-zykl neutralized lentiviral particles pseudotyped with EBOV GP (Makona variant) in HEK293 cells with an EC_{50} value of 0.15 μg/mL
- Ansuvimab-zykl neutralized wild-type EBOV (Mayinga variant) with an EC_{50} value of 0.06 μg/mL as determined by plaque reduction assay performed in Vero E6 cells.
- Ansuvimab-zykl mediated ADCC with maximal activity observed at a mAb concentration of 0.03 μg/mL.

Table 7. Summary of Cell Culture Antiviral Activity Data for Ansuvimab-zykl

	Live Virus PRA (EC_{50} Value) (μg/mL)			Pseudotype Virus (EC_{50} Value) (μg/mL)			ADCC Signaling HEK293/Tet-on/	
Antibody	**Kikwit**	**Makona**	**Mayinga**	**Kikwit**	**Makona**	**Mayinga**	**EBOV GP (μg/mL)**	**C1q Binding**
Ansuvimab-zykl	NA	NA	0.06	NA	0.15	0.09	0.03	No

Source: Review team analysis
Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; EBOV, *Zaire ebolavirus*, GP, glycoprotein; NA, not assessed; PRA, plaque reduction assay

Nonhuman Primate EBOV Lethal Challenge Studies

- Challenge experiments in rhesus macaques were performed with 1,000 PFU intramuscular (IM) injection with EBOV Kikwit variant. Of note, United States Army Medical Research Institute of Infectious Diseases (USAMRIID) investigators were blinded to the investigational antibodies but not treatment status.
- The challenge stock (AIMS 22955/RIID R4368; passage 4) contained a P430L polymorphism in the GP compared to Kikwit 1995 strain"134" (GenBank #AY354458) (Kugelman et al. 2016); however, the T544I polymorphism associated with other challenge stocks was not detected in the R4368 (passage 4) challenge stock. Of note, the R4368 (passage 4) challenge stock was predominantly 8U (85%) at the time of challenge; however, the Applicant noted that data from a previous study indicate that the 7U:8U genotype ratio shifts over the first few days of in vivo EBOV infection, resulting in ~90% 7U genotype (Kugelman et al., 2015). The Applicant concluded that the major genotype of circulating virus would likely be 7U in the NHP study by Day 5 post-infection when ansuvimab-zykl treatment was initiated in two of the studies. It is not clear if the 7U:8U genotype ratio shifts over the first few days of in vivo EBOV infection, resulting in ~90% 7U genotype, are representative of a direct 7U challenge. Use of a predominantly 8U virus stock may effectively result in a delay of the disease course. Clinical Virology recommended that the Applicant assess the antiviral activity of ansuvimab-zykl in a blinded NHP challenge study using a predominantly 7U challenge stock.
- The highest dose assessed in NHPs was 50 mg/kg ansuvimab-zykl administered as a single dose 1 (n=3) or 5 (n=3) days after challenge, or three doses (n=3) administered 1, 2, and 3 days after challenge. All nine of the NHPs that received the 50 mg/kg dose at the various dosing days survived the EBOV Kikwit challenge and none of the control animals survived (mean time-to-death =9.33 days).
- Lower doses were also assessed. All three NHPs treated with a dose of 30 mg/kg ansuvimab-zykl administered as a single dose 5 days (n=3) after challenge survived the

EBOV Kikwit challenge whereas the control animal was euthanized 10 days after infection.

A dose-down study was performed to assess three lower doses, including 1 (n=3), 2(n=3), 5 (n=3), or 15 (n=3) mg/kg of ansuvimab-zykl administered 1, 2, and 3 days after challenge. For all dose groups, two-thirds of the animals survived the EBOV Kikwit challenge whereas the control animals (n=2) were euthanized 8 and 9 days after challenge. Of note, the 5 mg/kg dose administered 1, 2, and 3 days after challenge was assessed in two independent studies with three NHPs in each but had variable results with 3/3 NHPs surviving the EBOV Kikwit challenge in one group but only 1/3 NHPs surviving challenge in the second group (Table 8).

Table 8. Summary of NHP Challenge Studies Performed With Ansuvimab-zykl

Study	Substudy	Group	Days After Challenge	Size (n)	Treatment	Dose (mg/kg)	NHP	Death (Day)	EBOV Titer GE/mL (Day)	Survivors (%)	MTD in Days (n)
RB-NCR-001	Study 1	Control	NA	1	None	0	14089	10	Und (1)	0/1 (0)	10 (1)
		ansuvimab-zykl, 50 mg	1	3	ansuvimab-zykl	50	13175	28	Und (1)	3/3 (100)	28 (3)
							14031	28	Und (1)		
							14059	28	Und (1)		
	Study 2	Control	NA	1	None	0	14151	9	Und (1)	0/1 (0)	9 (1)
		ansuvimab-zykl, 50 mg	5	3	ansuvimab-zykl	50	14117	28	Und (3)	3/3 (100)	28 (3)
							14081	28	36,900 (3)		
							13207	28	Und (3)		
	Study 3	Control	NA	1	None	0	NP	10	NP	0/1 (0)	10 (1)
		ansuvimab-zykl, 30 mg	5	3	ansuvimab-zykl	30	NP	28	NP	3/3 (100)	28 (3)
							NP	28	NP		
							NP	28	NP		
RB-NCR-002	Study 1	Control	NA	1	None	0	A12V075	9	Und (1)	0/1 (0)	9 (1)
		ansuvimab-zykl, 50 mg	Days 1, 2, and 3	3	ansuvimab-zykl	50	A13V031	28	Und (1)	3/3 (100)	28 (3)
							A12V113	28	Und (1)		
							A12V112	28	Und (1)		
		ansuvimab-zykl, 15 mg	Days 1, 2, and 3	3	ansuvimab-zykl	15	A12V054	28	Und (1)	3/3 (100)	28 (3)
							A12V130	28	Und (1)		
							A12V031	28	Und (1)		
		ansuvimab-zykl, 5 mg	Days 1, 2, and 3	3	ansuvimab-zykl	5	A13V012	28	Und (1)	3/3 (100)	28 (3)
							A12V160	28	Und (1)		
							A13V014	28	Und (1)		
	Study 2	Control	NA	1	None	0	NP	8	NP	0/1 (0)	8 (1)
		ansuvimab-zykl, 5 mg	Days 1, 2, and 3	3	ansuvimab-zykl	5	NP	NP	NP	1/3 (33)	10.5 (2)
							NP	NP	NP		
							NP	NP	NP		
		ansuvimab-zykl, 2 mg	Days 1, 2, and 3	3	ansuvimab-zykl	2	NP	NP	NP	2/3 (67)	9 (1)
							NP	NP	NP		
		ansuvimab-zykl, 1 mg	Days 1, 2, and 3	3	ansuvimab-zykl	1	NP	NP	NP	2/3 (67)	9 (1)
							NP	NP	NP		

Source: Review team analysis
Abbreviations: EBOV, *Zaire ebolavirus*; GE, genome equivalent; MTD, mean time to death; NA, not applicable; NHP, nonhuman primates; NP, not provided; Und, undetermined

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

A single dose of 50 mg/kg of ansuvimab-zykl was evaluated in the PALM Trial.

The human dosing regimen (a single dose of 50 mg/kg) was based on the results from lethal challenge studies in an exploratory NHP model (Section 5.1). These studies indicated that a single 50 mg/kg or 30 mg/kg dose of ansuvimab-zykl administered as late as 5 days postchallenge fully protected rhesus macaques from EBOV disease, thus preventing mortality. In contrast, all control animals in these studies succumbed to EBOV disease within 10 days.

We compared exposures in NHPs and humans to assess whether human exposures were expected to be similar to or exceed those associated with the effective dose in NHPs. Relative to uninfected NHPs administered 50 mg/kg, 50 mg/kg administered to uninfected humans resulted in 1.4-fold higher exposures. Assuming a similar impact of infection on PK in NHPs and humans, the PK data in uninfected NHPs and humans provided support for the single 50 mg/kg dose evaluated in the PALM Trial.

The dose selected for the PALM Trial was reasonable and was demonstrated to be effective in comparison to the active control. A higher dose of ansuvimab-zykl may provide additional benefit to patients infected with EBOV and with high baseline viral loads (Section 6.3.2). Of note, PK in infected humans was not evaluated in the PALM Trial, precluding evaluation of exposure-response relationships for efficacy or safety.

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Trial Design

The PALM Trial was designed as a master protocol and serves as the primary basis for the efficacy assessment. There are several advantages for implementing a master protocol design, including the ability to: 1) allow for the evaluation of multiple investigational treatments compared to a shared active investigational control arm, 2) add or remove arms, 3) reduce the sample size, and 4) use a common infrastructure with consistent data collection. While there is no consensus across the statistical community, many suggest that a master protocol does not require adjustment for multiple comparisons among treatment groups (Woodcock and LaVange 2017) because each comparison can be considered a separate trial. In the PALM Trial, the three investigational treatment arms belonged to different sponsors. Each sponsor did not have multiple chances to “win,” therefore no multiplicity adjustment was deemed necessary.

The trial began with the evaluation of two investigational treatment arms compared to a shared active investigational control arm (ZMapp), and subjects were randomized at a 1:1:1 ratio (refer to Section 6.3.1). On January 26, 2019, REGN-EB3 was added as the fourth investigational treatment arm, and subjects were subsequently randomized at a 1:1:1:1 ratio. Although the trial was open-label, the trial sponsor (NIAID) incorporated two randomization block sizes to prevent clinicians charged with administering the study drugs from guessing which drug would be

administered, thus reducing the potential for selection bias by staff members at Ebola treatment units (ETUs).

The trial initially targeted 125 subjects per arm based on an expected 28-day mortality rate of 30% in the ZMapp group, with a 50% relative reduction in the experimental treatment. The expected mortality rate of 30% in the ZMapp plus oSOC control arm was based, in part, on a meta-analysis of eight clinical studies conducted during the 2014 to 2016 West African Ebola outbreak. This meta-analysis indicated that mortality rates within PREVAIL II (NCT02363322, a randomized controlled trial designed to assess the efficacy of ZMapp), were lower than in other studies across both the treatment and control arms. Hence, the expected mortality rate with ZMapp in the PALM Trial could be anticipated to be higher than the point estimate from PREVAIL II. On July 17, 2019, an amendment was submitted to the NIAID and DRC ethics boards requesting enlargement of the sample size to 725 to increase power and allow for detection of a smaller, but clinically meaningful, treatment effect than the original assumed 50% decrease in mortality rate.

On August 9, 2019, the DSMB recommended stopping PALM before the planned enrollment was met and also recommended the Extension Phase commence with only ansuvimab-zykl and REGN-EB3 (Inmazeb), because a superiority finding for ansuvimab-zykl and REGN-EB3 over the active investigational control arm (ZMapp) was demonstrated. As a result, only 684 subjects were enrolled; they form the basis of the efficacy assessment (Mulangu et al. 2019).

Randomization was stratified by reverse-transcriptase polymerase chain reaction (RT-PCR) cycle threshold for CtNP ≤22.0 versus >22.0, Ebola Treatment Unit, and outbreak (however, all subjects were enrolled within a single outbreak). The selection of a CtNP threshold value of 22.0 was based on prior analysis of the distribution of CT values from a large cohort of Ebola virus-infected individuals during the 2014 to 2016 West African crisis. There were 4 ETUs in this study. Data will be presented as overall and by ETU. This review focuses only on subjects randomized to ansuvimab-zykl compared to ZMapp.

The primary efficacy endpoint was the 28-day mortality rate. Additional design information is available in Section 15.

6.2.2. Eligibility Criteria

Males or females of any age with documented positive RT-PCR (Cepheid assay) for acute EBOV infection within 3 days prior to enrollment and who had symptoms of any duration were eligible for the trial. Neonates (defined as ≤7 days old) born to a mother who was RT-PCR–positive for acute EBOV were presumed to be RT PCR–positive for acute EBOV at delivery and were eligible for enrollment even prior to RT-PCR confirmation (i.e., obtaining those results could lead to unnecessary delay). Subjects must have agreed not to enroll in another study of an investigational agent prior to completion of Day 28 of the study.

Subjects who had prior treatment with any investigational antiviral drug therapy against EBOV infection within five half-lives or 30 days, whichever was longer, prior to enrollment were not eligible to enroll in the study. Prior vaccination for prevention of EBOV was permitted.

See Section 15 for key inclusion and exclusion criteria.

6.2.3. Statistical Analysis Plan

The primary efficacy analysis compared ansuvimab-zykl to ZMapp using Boschloo's exact test. The analysis was conducted on the concurrent intent-to-treat (cITT) population. This population included all randomized subjects, except those who were subsequently randomized to another drug when the original drug was either unavailable or quarantined. The subjects were analyzed based on the randomized treatment.

As stated in the protocol, most clinical trials that intend to provide definitive evidence of efficacy ensure strict control of the two-sided type 1 error rate at an alpha level of 0.05, with adjustments for multiple comparisons of arms. This necessitates large sample sizes to ensure high power. The circumstances of high mortality, intermittent and small outbreaks, along with the need to identify effective treatments as quickly as possible justify less austere statistical penalties. As a result, the primary analysis comparing each investigational treatment arm to the shared investigational control arm used a two-sided alpha of 0.05 allocated over interim and final analyses.

An independent DSMB actively monitored interim data to make recommendations about early study closure or changes to study arms. During the fourth interim analysis, the trial results crossed the prespecified efficacy boundary and the DSMB decided to stop dosing with ZMapp and another treatment (remdesivir), but to continue ansuvimab-zykl and the other treatment arm (REGN-EB3). At this point, 499 participants were enrolled with at least 10 days of follow-up. The 10-day mortality rate was utilized because it was similar to the 28-day mortality rate. This was verified by the final analysis results, which showed that most subjects died on or before the first 11 days.

The final analysis occurred at the fifth interim analysis, and the corresponding interim monitoring boundary was used to assess significance. Thus, a p-value of <0.028 (two-sided) for the comparison of ansuvimab-zykl to ZMapp was required to claim statistical significance for the primary endpoint.

For more details, please refer to Section 15.

6.2.4. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients

This section summarizes the subject disposition, baseline demographics, clinical characteristics, and primary and key secondary efficacy results to support the efficacy of ansuvimab-zykl in reducing 28-day mortality over ZMapp in subjects with confirmed *Zaire ebolavirus* disease.

6.2.4.1. Disposition, Baseline Demographics, and Baseline Clinical Characteristics

Disposition

In the PALM Trial, 684 subjects were enrolled, and three enrolled subjects died before randomization. In total, there were 681 subjects randomized. Among randomized subjects, 176 subjects were randomized to the ansuvimab-zykl arm and 169 were randomized to the ZMapp arm. These 345 subjects comprised the overall intent-to-treat (oITT) population. Three subjects were excluded from the oITT population, resulting in 342 subjects in the primary efficacy

analysis population (the concurrent or cITT population). The reasons for exclusion of the three subjects were that two subjects were randomized to ansuvimab-zykl when ZMapp was not available, and one subject was randomized to ZMapp when REGEN-EB3 was not available. Additional details are provided in Section 16.2.

Table 9. Subject Screening and Randomization, PALM Trial

Analysis Population	Ansuvimab-zykl	ZMapp	Total
Subjects died before randomization	–	–	3
Overall randomized (oITT)	176	169	345
Randomized but died before receiving study drug	3	1	4
Subjects randomized during a drug shortage of either Ansuvimab-zykl or ZMapp	2	1	3
Randomized and treated	173	168	341
cITT analysis population	174	168	342
Safety analysis population	173	168	341

Source: Statistical reviewer, ADSL
Abbreviations: cITT: concurrent ITT; ITT, intent-to-treat; oITT: overall ITT; PALM, PAmoja TuLinde Maisha

Subject disposition information for the intent-to-treat (ITT) population following Amendment 3 (ITT Amd 3) is summarized in Table 9. By Day 28, 61 (35.1%) subjects randomized to ansuvimab-zykl had died, and 83 (49.4%) subjects randomized to ZMapp had died. One subject in each arm died after Day 28 but before Day 58. The percentage of subjects completing Day 58 was 64.8% in the ansuvimab-zykl arm and 49.7% in the ZMapp arm.

Table 10. Disposition, PALM Trial

Disposition (oITT)	Ansuvimab-zykl	ZMapp	Total
All randomized (oITT)	176	169	345
Positive baseline CtNP	176	168*	344
Negative baseline CtNP	0	0	0
Subjects completed day 28 visit	115 (65.3%)	85 (50.3%)	200
Subjects died before day 28	61 (34.7%)	84 (49.7%)	145
Subjects completed day 58 visit	114 (64.8%)	84 (49.7%)	198
Subjects died before day 58	62 (35.2%)	85 (50.3%)	147

Source: Statistical reviewer, ADSL
* One subject in the ZMapp arm did not have baseline CtNP measurement.
Abbreviation: CtNP, cycle-threshold nucleoprotein gene targets; ITT, intent-to-treat; oITT, overall randomized intention-to-treat analysis population; PALM, PAmoja TuLinde Maisha

Baseline Demographics and Clinical Characteristics

The subjects' demographic characteristics were similar in the two arms. Overall, slightly more female subjects (54.1%) were enrolled compared to male subjects (45.9%) and the median age was 26 years, with a range of 1 day to 85 years. Most subjects (84.7%) were enrolled at the Beni and Butembo sites. The other two sites, Katwa and Mangina, enrolled only 15.2% of the subjects. A baseline CtNP >22 (low viral load) was observed in 57.9% of subjects, 22.5% of subjects self-reported having received vaccination (a recombinant vesicular stomatitis virus expressing the EBOV glycoprotein, or rVSV-ZEBOV) prior to baseline, and 7.3% of subjects were malaria positive at baseline. The overall median number of days from symptom onset to randomization was 5 days.

Table 11. Baseline Demographic and Clinical Characteristics, ITT Concurrent Population, PALM Trial

Characteristics	Ansuvimab-zykl (N=174)	ZMapp (N=168)	Total (N=342)
Sex, n (%)			
Female	98 (56.3%)	87 (51.8%)	185 (54.1%)
Male	76 (43.7%)	81 (48.2%)	157 (45.9%)
Age (year)			
Mean (SE)	27.3 (1.4)	29.9 (1.3)	286 (1.0)
Median	26.0	27.5	26.0
Range	(0.0, 85.0)	(0.0, 70.0)	(0.0, 85.0)
SD	18.7	16.7	17.8
Age category 1, n (%)			
<18 years	54 (31.0%)	33 (19.6%)	87 (25.4%)
≥18 years	120 (69.0%)	135 (80.4%)	255 (74.6%)
Age category 2, n (%)			
0 to <1 month	4 (2.3%)	2 (1.2%)	6 (1.8%)
1 month to <1 year	7 (4.0%)	5 (3.0%)	12 (3.5%)
1 year to <6 years	15 (8.6%)	12 (7.1%)	27 (7.9%)
6 years to <12 years	13 (7.5%)	5 (3.0%)	18 (5.3%)
12 years to <18 years	15 (8.6%)	9 (5.4%)	24 (7.0%)
18 years to <50 years	93 (53.4%)	114 (67.9%)	207 (60.5%)
50 years to <65 years	21 (12.1%)	18 (10.7%)	39 (11.4%)
≥65 years	6 (3.4%)	3 (1.8%)	9 (2.6%)
Site, n (%)			
Beni	87 (50.0%)	83 (49.4%)	170 (49.7%)
Butembo	60 (34.5%)	60 (35.7%)	120 (35.1%)
Katwa	12 (6.9%)	12 (7.1%)	24 (7.0%)
Mangina	15 (8.6%)	13 (7.7%)	28 (8.2%)
CtNP at screening, n (%)			
≤22	73 (42.0%)	70 (41.7%)	143 (41.8%)
>22	101 (58.0%)	97 (57.7%)	198 (57.9%)
Unknown		1 (0.6%)	1 (0.3%)
Baseline CtNP			
n	174	167	341
Mean (SE)	24.60 (0.483)	23.44 (0.401)	24.03 (0.316)
Median (Q1, Q3)	23.25 (19.7, 28.5)	23.10 (19.0, 26.5)	23.1 (19.3, 27.1)
Range	(12.80, 42.50)	(14.80, 37.20)	(12.80, 42.50)
SD	6.371	5.181	5.839
Reported cVSV-ZEBOV vaccination, n (%)			
Y	36 (20.7%)	41 (24.4%)	77 (22.5%)
N	121 (69.5%)	112 (66.7%)	233 (68.1%)
Unknown	17 (9.8%)	15 (8.9%)	32 (9.4%)
Ebola vaccination in days category			
n	36	41	77
<10 days	22 (61.1%)	21 (51.2%)	43 (55.8%)
≥10 days	12 (33.3%)	18 (43.9%)	30 (39.0%)
Unknown	2 (5.6%)	2 (4.9%)	4 (5.2%)
Malaria status			
Positive	13 (7.5%)	12 (7.1%)	25 (7.3%)
Negative	127 (73.0%)	127 (75.6%)	254 (74.3%)
Unknown	34 (19.5%)	29 (17.3%)	63 (18.4%)

Characteristics	Ansuvimab-zykl (N=174)	ZMapp (N=168)	Total (N=342)
Days from symptom onset to randomization			
n	174	167	341
Mean (SE)	5.5 (0.27)	5.6 (0.28)	5.5 (0.19)
Median (Q1, Q3)	5 (3, 7)	5 (3, 7)	5 (3, 7)
Range	(0, 20)	(1, 21)	(0, 21)
SD	3.6	3.6	3.6
Pregnancy test positive			
n	98	87	185
Positive	5 (5.1%)	4 (4.6%)	9 (4.9%)
Baseline ALT (U/L)			
n	141	130	271
Mean (SE)	357.1 (36.65)	408.0 (41.73)	381.5 (27.64)
Median (Q1, Q3)	168.0 (44, 551)	235.5 (48, 631)	193.0 (44, 604)
Range	(12, 1960)	(5, 2000)	(5, 2000)
SD	435.2	475.8	455.0
Baseline AST (U/L)			
n	99	89	188
Mean (SE)	519.6 (58.90)	711.0 (74.98)	610.2 (47.53)
Median (Q1, Q3)	234 (66, 978)	351 (112, 1404)	270 (83.5, 1094.5)
Range	(27, 2000)	(29, 2000)	(27, 2000)
SD	586.1	707.4	651.7
Baseline creatinine (mg/dL)			
n	143	127	270
Mean (SE)	2.06 (0.217)	2.87 (0.297)	2.44 (0.182)
Median (Q1, Q3)	0.90 (0.6, 2.4)	1.20 (0.8, 4.3)	1.00 (0.7, 3.1)
Range	(0.2, 12.9)	(0.3, 17.4)	(0.2, 17.4)
SD	2.592	3.350	2.995

Source: Statistical reviewer, ADSL and SAS software used
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CtGP, cycle-threshold glycoprotein gene targets; CtNP, cycle-threshold nucleoprotein gene targets; ITT, intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; PALM, PAmoja TuLinde Maisha; rVSV, vesicular stomatitis virus; SD, standard deviation; SE, standard error

6.2.4.2. Primary and Key Secondary Efficacy Results

Primary Efficacy Endpoint

The Applicant's primary efficacy results were confirmed by the statistical review team and demonstrated superiority of ansuvimab-zykl compared to ZMapp in reducing the 28-day mortality rate in subjects with confirmed *Zaire ebolavirus* infection (Table 12). The difference in 28-day mortality rate between ansuvimab-zykl and ZMapp was -14.4% (95% CI: -24.8, -2.4).

Of note, the 95% CI and Boschloo's two-sided p-value generated by the reviewer were slightly different from those of the Applicant due to the software used for the analyses. The Applicant used R and the statistical reviewer used Statistical Analysis System. The differences were negligible and did not change the conclusion of the trial. The Applicant's results were used in the label.

Table 12. Summary of 28-Day Mortality in the Primary Efficacy Analysis, Concurrent ITT Population, PALM Trial*

Population	Ansuvimab-zykl (N=174) Death/Total (%)	ZMapp (N=168) Death/Total (%)	Rate Difference % (95% CI)[a]	Boschloo's Two-Sided P-Value[b]
Concurrent ITT	61/174 (35.1%)	83/168 (49.4%)	-14.4 (-24.8, -2.4)	0.0075

Source: Statistical reviewer, ADSL and SAS software were used.
[a] The exact confidence interval was based on inverting two one-sided tests in StatXact.
[b] P-value based on Boschloo's test with a default gamma of 0 in StatXact.
* The 95% CI and two-sided P-value are slightly different from the Applicant's due to the software used for the analysis; the differences do not affect the conclusion of the trial. The Applicant used R and Barnard's exact test in SAS as the Applicant stated that the p-values from Barnard's exact test in SAS matched p-values from Boschloo's exact test in R to decimals. The statistical reviewer used SAS StatXact Proc package. The Applicant's results were used in the label.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects; PALM, PAmoja TuLinde Maisha

Sensitivity Analyses of the Primary Efficacy Endpoint

The primary efficacy endpoint results were consistent across different analysis populations with the exception of the not cITT2 population where the sample sizes were very small and the 28-day mortality rates of the two arms were similar (Table 13). The definitions of the analysis populations were as follows:

- Overall ITT included all randomized subjects
- cITT2 included all cITT subjects excluding 32 subjects who were randomized before January 26, 2019
- cITT3 included all cITT subjects excluding six subjects who were originally randomized to the ZMapp arm and were re-randomized to ansuvimab-zykl or REGN-EB3 at the end of the randomization phase
- Treated included all oITT subjects excluding four subjects who died before being treated
- Not cITT2 included all cITT subjects excluding subjects who randomized after January 26, 2019.

Table 13. Summary of 28-Day Mortality in Different Analysis Populations, PALM Trial

Population	Ansuvimab-zykl Death/Total (%)	ZMapp Death/Total (%)	Rate Difference % (95% CI)[a]	Boschloo's Two-Sided P-Value[b]
Concurrent ITT	61/174 (35.1%)	83/168 (49.4%)	-14.4 (-24.8, -2.4)	0.0075
Overall ITT	61/176 (34.7%)	84/169 (49.7%)	-15.1 (-25.4, -2.8)	0.0054
cITT2	55/157 (35.0%)	78/153 (51.0%)	-16.0 (-26.8, -3.1)	0.0050
cITT3	61/174 (35.1%)	82/162 (50.6%)	-15.6 (-26.1, -3.0)	0.0036
Treated	58/173 (33.5%)	83/168 (49.4%)	-15.9 (-26.2, -3.6)	0.0026
NcITT2	6/17 (35.3%)	5/15 (33.3%)	2.0 (-32.0, 35.7)	1.0

Source: Statistical reviewer, ADSL and SAS software were used
[a] The exact confidence interval was based on inverting two one-sided tests in StatXact.
[b] P-value based on Boschloo's test with a default gamma of 0 in StatXact.
Abbreviations: APT, all patients treated; CI, confidence interval; ITT, intent-to-treat; PALM, PAmoja TuLinde Maisha

Secondary Efficacy Endpoints

Mortality distributed by study day was a key secondary endpoint. Most deaths, 47/62 (75.8%) in the ansuvimab-zykl arm and 62/84 (73.8%) in the ZMapp arm, occurred within the first 4 days of the trial (Table 14). With four exceptions, all deaths occurred within the first 10 days. One death in the ansuvimab-zykl arm occurred on Day 13, and one death in the ZMapp arm occurred on Day 18. From Day 28 to Day 58, there were two deaths, one in each arm.

Table 14. Number of Deaths by Study Day, Concurrent ITT Population, PALM Trial

Parameter	Ansuvimab-zykl (N=174)	ZMapp (N=168)
Total number of subjects who died, n (%)	62 (35.6)	84 (50.0)
Study day of death, n (%)		
Day 1	6 (3.4)	14 (8.3)
Day 2	16 (9.2)	18 (10.7)
Day 3	19 (10.9)	21 (12.5)
Day 4	6 (3.4)	9 (5.4)
Day 5	5 (2.9)	4 (2.4)
Day 6	3 (1.7)	7 (4.2)
Day 7	3 (1.7)	4 (2.4)
Day 8	0	3 (1.8)
Day 9	1 (0.6)	1 (0.6)
Day 10	1 (0.6)	1 (0.6)
Day 11	0	0
Day 12	0	0
Day 13	1 (0.6)	0
Day 14	0	0
Day 15	0	0
Day 16	0	0
Day 17	0	0
Day 18	0	1 (0.6)
Days 19 to 27	0	0
Day 28	0	0
Days 29 to 35	0	0
Day >35	1 (0.6)	1 (0.6)

Source: Statistical reviewer, ADSL and SAS software were used.
Abbreviations: ITT, intent-to-treat; N, number of subjects; n, number of subjects in subgroup; PALM, PAmoja TuLinde Maisha

The 58-day mortality rate was another key secondary efficacy endpoint (Table 15). The difference in 58-day mortality rate between ansuvimab-zykl and ZMapp was -14.4% (95% CI -24.8, -2.4), which is almost identical to the 28-day mortality rate.

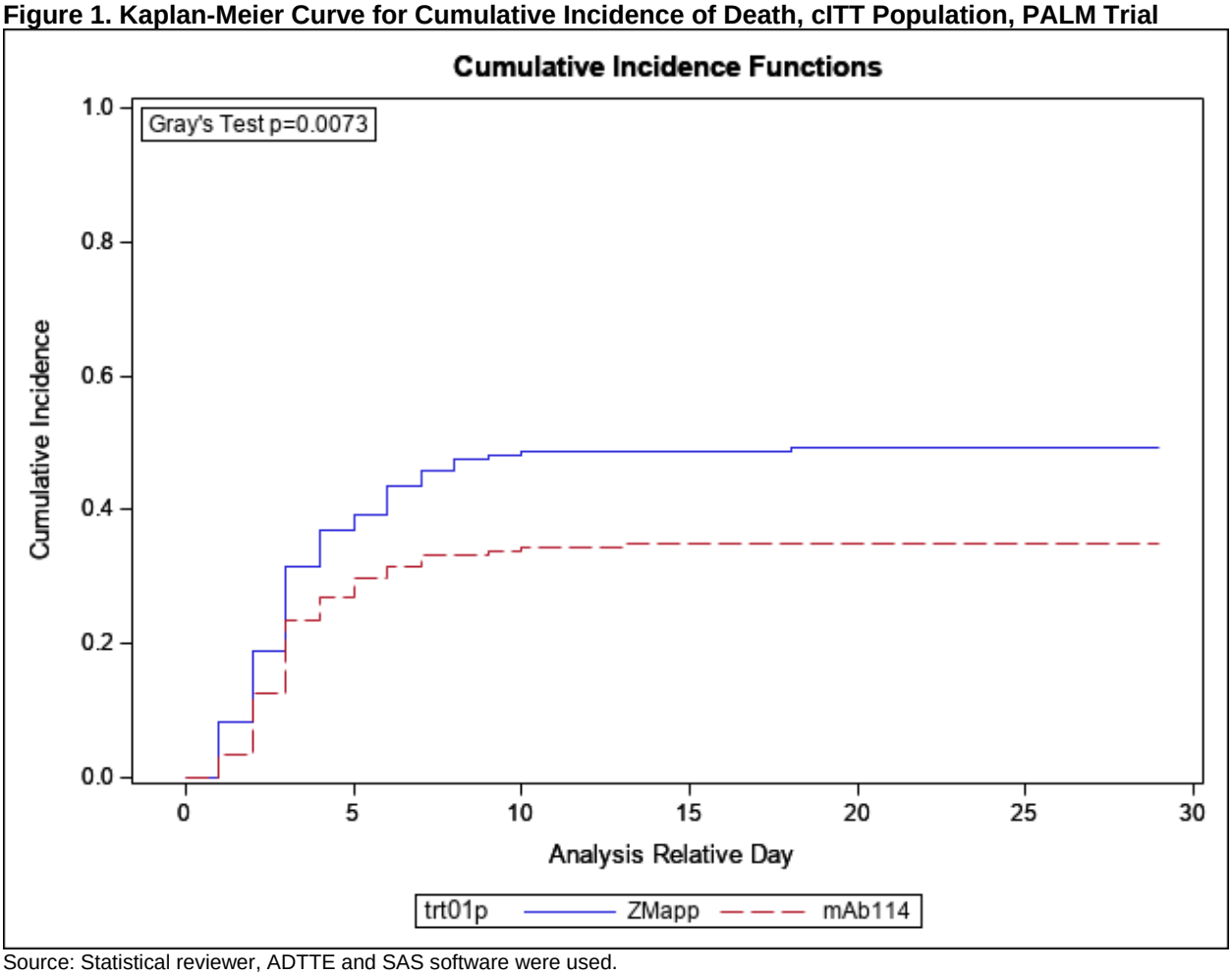
Table 15. Summary of 58-Day Mortality in the Primary Efficacy Analysis, Concurrent ITT Population, PALM Trial

Population / Subpopulation	Ansuvimab-zykl (N=174) n (%)	ZMapp (N=168) n (%)	Rate Difference % (95% CI)[a]	Boschloo's 2-Sided P-Value[b]
cITT at Day-58	62 (35.6%)	84 (50.0%)	-14.4 (-24.8, -2.4)	0.0077

Source: Statistical reviewer, ADSL and SAS software were used.
[a] The exact confidence interval was based on inverting two one-sided tests in StatXact.
[b] P-value based on Boschloo's test with a default gamma of 0 in StatXact.
Abbreviations: CI, confidence interval; cITT, concurrent ITT; ITT, intent-to-treat; PALM, PAmoja TuLinde Maisha

The Kaplan–Meier curve for the cumulative incidence of death is shown in Figure 1 below. Because most deaths occurred within the first 4 days, the cumulative incidence of death increased sharply in the first few days in both arms. After Day 4, the cumulative incidence of death in the ansuvimab-zykl arm remained lower than that in the ZMapp arm. The log-rank test indicated a significant difference in the curves over time (p=0.0072).

Figure 1. Kaplan-Meier Curve for Cumulative Incidence of Death, cITT Population, PALM Trial



Source: Statistical reviewer, ADTTE and SAS software were used.
Abbreviations: ITT, intent-to-treat; PALM, PAmoja TuLinde Maisha

6.2.4.3. Subgroup Analyses for the Primary Efficacy Endpoint

Analyses were conducted to assess the treatment effect for subgroups defined by various demographic and clinical characteristics at baseline. The treatment effect of ansuvimab-zykl compared to ZMapp appeared consistent across most baseline subgroups of age, gender, site, and other baseline factors analyzed. See Section 16 for details.

For alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine, the higher the baseline values over the upper limit of normal, the higher the 28-day mortality rate in both arms. Subjects who were treated within 5 days from symptom onset to randomization had lower 28-day mortality rates in both arms than those treated more than 5 days from symptom onset to randomization. In addition, the 28-day mortality rates in the ansuvimab-zykl arm were lower than those in the ZMapp arm across these subgroups. The impact of baseline viral load is discussed in Section 6.3.2.

Of note, the sample sizes for many subgroups were small, which limits the ability to detect trends with certainty. Numerous subgroup analyses were conducted without any adjustment for the multiple analyses, which could result in spurious findings due to chance.

6.3. Review Issues Relevant to the Evaluation of Benefit

The review team concluded that the results of the PALM Trial support the proposed indication. The review team did not identify any issues with assessing superiority of ansuvimab-zykl over ZMapp for the primary efficacy endpoint (28-day mortality); therefore, no further discussion is warranted in this subsection.

The review issues relevant to the evaluation of benefit focus on:

- Use of an investigational drug, ZMapp, as an active control versus oSOC alone
- Lower efficacy in ansuvimab-zykl-treated subjects with high viral loads (baseline CtNP values ≤22) versus subjects with low baseline viral loads (CtNP >22)
- Adequacy of clinical experience with pediatric subjects and inclusion of labeled recommendations for low-birth-weight neonates born to EBOV-infected mothers
- Lack of clinical experience with ansuvimab-zykl for treatment of EBOV infection acquired by routes other than natural transmission
- Use of an inadequately validated bioanalytical assay to measure serum concentrations of ansuvimab-zykl in the serum of healthy humans raised concerns about the reliability of the resulting PK data.

6.3.1. Use of an Investigational Drug, ZMapp, as an Active Control Versus Optimized Standard of Care Alone

Issue

Use of an investigational drug, ZMapp, as an active control versus oSOC alone raised concerns about the interpretability of results in the PALM Trial.

Background

ZMapp was previously investigated in the PREVAIL II trial but has not been approved in any country for the treatment of EBOV infection. During the development of the PALM Trial, the protocol allowed for country-specific preferences about what constitutes an ethical and scientifically acceptable control arm. Given the state of equipoise for ZMapp, the master protocol contained two options for the control arm as suggested by the WHO Research and Development Ebola Therapeutics Committee: either ZMapp plus oSOC or oSOC alone. The two options for the control arm resulted in two possible trial designs:

- Option 1: ZMapp as the control arm (four arms, ZMapp plus oSOC versus. Drug A plus oSOC versus. Drug B plus oSOC versus. Drug C plus oSOC)
- Option 2: oSOC alone as the control arm (five arms, oSOC versus. ZMapp plus oSOC versus Drug A plus oSOC versus. Drug B plus oSOC versus Drug C plus oSOC)

The decision about the appropriate control arm was at the discretion of the host country. The PALM Trial initially enrolled participants only in the DRC, which chose Option 1, with ZMapp plus oSOC as the control arm.

Assessment

In the PREVAIL II trial, eligible subjects of any age were randomly assigned at a 1:1 ratio to receive either the current oSOC or the current oSOC plus three intravenous (IV) infusions of ZMapp (50 mg/kg, administered every third day). Subjects were stratified according to their baseline RT-PCR cycle-threshold nucleoprotein gene target values (≤22 predicted a high viral load versus >22) and by country of enrollment. The primary endpoint was the 28-day mortality rate. Due to curtailing of the outbreak in that region and a desired accrual of 100 subjects per arm, a total of 72 subjects were enrolled at sites in Liberia, Sierra Leone, Guinea, and the United States. Of the 72 subjects enrolled, 71 were evaluated for the Day-28 mortality endpoint and were included in the analyses. Overall, 21 subjects died, for an overall case-fatality rate of 30%. Death occurred in 13 of 35 subjects (37%) who received the current oSOC alone and in 8 of 36 subjects (22%) who received the current oSOC plus ZMapp. The observed posterior probability that ZMapp plus the current oSOC was superior to the current oSOC alone was 91.2%, falling short of the prespecified threshold of 97.5%. Frequentist analyses yielded similar results (absolute difference in mortality with ZMapp, -15%; 95% CI: -36%, 7%). It was noted that the baseline viral load was strongly predictive of both mortality and duration of hospitalization in all age groups. Although the estimated effect of ZMapp appeared to be beneficial, the PREVAIL II trial result did not meet the prespecified statistical threshold for efficacy.

Table 16. Summary of Results, PREVAIL II

Mortality of ZMapp+oSOC	Mortality of oSOC Alone	Bayesian Analysis: Posterior Probability Threshold (97.5%) for Superiority	Absolute Difference in Mortality (95% CI)
8/36 (22%)	13/35 (37%)	91.2%	-15% (-36%, 7%)

Source: PREVAIL II Writing Group (PREVAIL II Writing Group 2016)
Abbreviations: CI, confidence interval; oSOC, optimized standard of care

In summary, in the PREVAIL II trial, ZMapp demonstrated a numerically favorable trend over oSOC alone but did not reach the level of statistical significance. Based on this information and given that the host country (DRC) preferred use of ZMapp + oSOC as the active control in the PALM Trial, it was reasonable to use ZMapp as the control in the study instead of using optimized standard of care alone.

Conclusion

Based on the preliminary experience with ZMapp in the PREVAIL II trial, the choice of ZMapp combined with oSOC is acceptable as an active control in the PALM Trial. Although PREVAIL II did not meet the prespecified threshold, and was unable to establish a noninferiority margin for mortality, the use of an active control in the PALM Trial was acceptable because of its superiority design. The results from the PALM Trial are therefore interpretable and the trial design is adequate to demonstrate superiority of ansuvimab-zykl over ZMapp in terms of improvement in the 28-day mortality rate when combined with oSOC.

6.3.2. Lower Efficacy in Subjects With a Baseline CtNP of 22 or Lower

Issue

Lower efficacy was observed in subjects with high baseline EBOV viral loads (RT-PCR CtNP ≤22) compared to subjects with low viral loads (CtNP >22) (although the rate difference in the high baseline viral load subgroup was similar to that of the overall ITT concurrent population); however, it is unknown whether a higher dose of ansuvimab-zykl would reduce mortality for those with high baseline EBOV viral loads. This section summarizes the evaluation of nonclinical data in support of the human dose selection, including the limitations of the available nonclinical virology data.

Background

Given the challenges of conducting adequate and well-controlled trials for treatment of EBOV infection, the development program for ansuvimab-zykl was initially based on fulfilling the necessary criteria for potential approval under the Animal Rule pathway. When the 2018 Eastern DRC outbreak occurred, the nonclinical program was progressing but was incomplete. However, the NHP data were sufficient to support the proof-of-concept and use of a single 50 mg/kg IV dose of ansuvimab-zykl in the PALM Trial and expanded access program. The NHP studies (rhesus macaques infected with EBOV) demonstrated improved survival of macaques treated with single doses of 30 mg/kg and 50 mg/kg compared to placebo (Section 5.1). The first study showed treatment with either single doses of 30 or 50 mg/kg, or up to 3 doses of ansuvimab-zykl when given as late as 5 days after an EBOV challenge protected macaques. Follow-up NHP studies showed that administration of a single 50 mg/kg or 30 mg/kg dose of ansuvimab-zykl up to 5 days postchallenge provided uniform protection from death (100% survival in animals receiving ansuvimab-zykl) (Section 5.1). The 50 mg/kg dose was selected as the clinical dose for treatment of patients infected with EBOV in the PALM Trial. At that time, the highest dose evaluated (50 mg/kg) was considered a reasonable dose for use in the PALM Trial based on the limited activity data in NHPs, PK in uninfected NHPs, and safety and PK in healthy subjects. PK in infected humans was not evaluated in the PALM Trial, precluding evaluation of exposure-response relationships for efficacy or safety.

Assessment

PALM Trial: Increased Mortality in Subjects With High Baseline Viral Loads

In the PALM Trial, ansuvimab-zykl was administered as a single IV infusion of 50 mg/kg, and subjects treated with this regimen had an overall mortality rate of 35.1% (61 of 174 subjects died) compared to 49.4% (83 of 168 subjects died) for the ZMapp control arm (p=0.008) (Table 17). As shown in Section 6.2.4, the baseline CtNP value was a stratification factor and the mortality rates for subjects who had high baseline viral loads (CtNP ≤22) were 69.9% for ansuvimab-zykl and 85.7% for the ZMapp control arm (Table 17). The mortality rate was 9.9% for subjects treated with ansuvimab-zykl who had lower baseline viral loads (CtNP >22) compared to 23.7% for the ZMapp control arm (Table 17). The trial results demonstrated that subjects who exhibited lower viral loads at baseline generally experienced better outcomes.

Despite the difference in mortality rates based on baseline CtNP values, ansuvimab-zykl was superior to ZMapp for both strata.

Table 17. Twenty-Eight-Day Mortality Rate by Baseline Viral Load, ITT Concurrent Population, PALM Trial

Population/ Subpopulation	Ansuvimab-zykl (N=174) Death/Total (%)	ZMapp (N=168) Death/Total (%)	Rate Difference % (95% CI)[a]	Boschloo's Two-Sided P-Value[b]
ITT concurrent	61/174 (35.1%)	83/168 (49.4%)	-14.4 (-24.8, -2.4)	0.0075
CtNP at baseline				
CtNP ≤22	51/73 (69.9%)	60/70 (85.7%)	-15.9 (-29.7, -1.7)	0.0227
CtNP >22	10/101 (9.9%)	23/97 (23.7%)	-13.8 (-24.5, -2.6)	0.0104

Source: Statistical reviewer, ADSL and SAS software were used.
[a] The exact confidence interval was based on inverting two one-sided tests in StatXact.
[b] P-value is based on Boschloo's test with a default gamma of 0 in StatXact.
Abbreviations: CI, confidence interval; CtNP, cycle-threshold nucleoprotein gene targets; ITT, intent-to-treat; N, number of subjects; PALM, PAmoja TuLinde Maisha

The multidisciplinary team analyzed all available data submitted by the Applicant to assess this review issue in detail. The Applicant has adequately demonstrated efficacy of 50 mg/kg of ansuvimab-zykl as a single IV dose for treatment of EBOV infection in humans, but the 60.0% absolute difference in mortality rates between subjects with high versus low baseline viral loads indicates that a higher dose may have the potential to provide additional benefit for patients who present with high baseline viral loads at the time of ansuvimab-zykl treatment.

Secreted Glycoprotein Binding

An important consideration for mAbs is whether or not they bind to secreted glycoprotein (sGP). sGP is the soluble, dimeric version of GP that results from the primary open reading frame of the *GP* gene and is expressed abundantly during EBOV infection (Sanchez et al. 1998). An insertion/deletion in the EBOV GP gene sequence is known to arise in the viral population after passage in cell culture resulting in an insertion of a uridine at the poly-U site at position 6918 to 6924, shifting it from a 7U to an 8U genotype. This change occurs within 24 hours postinfection in cell culture and, as a result, flips the normal production ratios of sGP:GP such that GP is now the dominant product made with the 8U genotype (Volchkov et al. 1995; Kugelman et al. 2012). Importantly, mAbs that bind sGP may not be as effective in protecting against infection, because sGP could serve as a decoy for mAbs that might otherwise bind viral particles (Murin et al. 2014). Of note, ansuvimab-zykl binds to sGP, but the impact of this binding has not been characterized and the NHP model is not likely to be robust enough for such assessments due to the highly variable nature of EBOV infection in NHPs.

Conclusion

The Applicant adequately demonstrated the efficacy of 50 mg/kg of ansuvimab-zykl as a single IV dose for treatment of EBOV infection in humans. A higher dose of ansuvimab-zykl may provide additional benefit to patients who are infected with EBOV and present with high baseline viral loads. Given the limitations of the EBOV NHP challenge model, the review team concluded that additional NHP studies are unlikely to provide further evidence to support use of a higher dose in patients with EBOV infection and high baseline viral loads. Therefore, the review team reached consensus that a postmarketing commitment (PMC) would be communicated to the Applicant to request further dose optimization for ansuvimab-zykl for patients with high baseline viral loads. In the PMC, we acknowledged the reliance on third

parties to conduct such a trial and requested the Applicant collaborate with US public health agencies, other public health agencies and local health authorities, as appropriate. The review team will work with the Applicant to develop a protocol that could be implemented should there be a future EBOV outbreak.

6.3.3. Adequacy of Clinical Experience With Pediatric Subjects and Inclusion of Labeling for Neonates Born to EBOV-Infected Mothers

Issue

Although the PALM Trial and MEURI EAP included subjects of all ages, including neonates born to mothers infected with EBOV, there was limited experience with subjects less than 18 years of age, particularly with neonates less than 1 month of age. Additionally, while ansuvimab-zykl dosing recommendations are based on weight, there remains a lack of PK data from infected subjects to inform optimal dosing for all weight ranges.

Background

On May 8, 2019, ansuvimab-zykl was granted Orphan Drug Designation (#2019-6830) for the treatment of patients with EBOV infection. With this designation, Pediatric Research Equity Act requirements were exempted. Nevertheless, given the anticipated benefit (supported by initial NHP studies) and the high mortality rate associated with untreated EBOV infection, the weight-based dose rationale was considered acceptable for enrollment of pediatric subjects, regardless of age or weight, in the PALM Trial and MEURI EAP. Neonates ≤7 days of age were eligible if the mother had documented infection, including if the mother had cleared her infection but the investigator thought the neonate was likely to be infected.

Assessment

Table 18 shows enrollment by age group in the PALM Trial and the MEURI EAP. Overall, 132 subjects (31%) of the combined population were in pediatric age groups.

Table 18. Subjects Treated With Ansuvimab-zykl by Age Group, PALM Trial and MEURI EAP

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

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

The primary review division, Division of Antivirals (DAV), placed an interoffice neonatal-perinatal medicine consultation request to the Office of Pediatric Therapeutics, OCPP/OC. In her responding memorandum, Gerri Baer, MD, noted that in the PALM Trial, 54 of the 174 subjects

(31%) who received ansuvimab-zykl were <18 years of age, with the largest proportion (n=26) <6 years of age. Four subjects were <1 month of age, and seven subjects were 1 month to <1 year of age. Of the 4 enrolled neonates, two died. One was 18 days old (died one day after treatment from complications of EBOV disease), and one died on Day 45 from severe malnutrition, after recovering from EBOV and discharge from the hospital. The mortality rate by age group in the PALM Trial is shown in Table 19. Overall, the mortality rate was consistent in pediatric patients <18 years of age (37%) and adult (34%) subjects.

Table 19. Mortality Rate, PALM Trial

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

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

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

Conclusion

Overall, ansuvimab-zykl demonstrated a significant mortality benefit over an active control in the pediatric population. Because the PALM Trial included a neonate with a weight down to 2 kg, the primary review team asked the Office of Pediatric Therapeutics to comment on the inclusion of a minimum weight in the product indication, specifically inclusion of extremely low-birth-weight neonates given available study data. DAV and the Office of Pediatric Therapeutics agreed that the Ebanga label should provide dosing and administration information to address all populations for which the potential benefits of the product outweigh the potential risks, including preterm neonates with a minimum weight of 0.5 kg.

Specific safety concerns related to dosing and administration are further discussed in Section 7.7.3 as review issues related to the assessment of risk.

6.3.4. Lack of Clinical Experience With Ansuvimab-zykl for Treatment of EBOV Infection Acquired by Routes Other Than Natural Transmission

Issue

The proposed indication for Ebanga (ansuvimab-zykl) is “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.” There is the potential for this drug to be used in

the United States to treat other transmission routes, for example an occupational exposure or by intentional release. However, the PALM Trial and MEURI EAP treated subjects infected with EBOV who were presumably infected via the natural EBOV transmission route (i.e., contact with infected blood or body fluids).

Background

Clinical data for ansuvimab-zykl efficacy are limited to presumed natural-infection of EBOV, although additional data from occupational exposures acquired during the MEURI EAP may be available in the future.

Studies in lethal NHP challenge models of EBOV have indicated that the 50 mg/kg dose of ansuvimab-zykl administered by IV 5 days after challenge with 1,000 PFU of EBOV (8U) administered by IM injection reduces mortality (Section 5.1); however, it is possible that a clinical needlestick accident may result in a much higher exposure than the 1,000 PFU challenge dose (Hwang 2014; Geisbert et al. 2015).

Nonclinical studies would be needed to support efficacy for an intentional release and would depend on the type of release (i.e., route of exposure, exposure dose, etc.).

Assessment

The review team discussed this issue at length, and considered potential label changes (in red) to address the final wording of the indication, including:

1. **Changing the indication:** Ebanga (ansuvimab-zykl) is a *Zaire ebolavirus* glycoprotein-directed human monoclonal antibody indicated for the treatment of naturally acquired 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.
2. **Adding a limitation of use:** The efficacy of Ebanga has not been established for *Zaire ebolavirus* infection caused by unnatural routes of exposure (i.e., needlestick, or intentional release)

(b) (4)

Conclusion

Clinical Review Team Perspective

The consensus of the Clinical review team for ansuvimab-zykl was to not address this issue with a Limitation of Use statement or with a modification to the indication in the proposed label. The Clinical review team agreed that although the NHP studies were inadequate to demonstrate evidence of efficacy in the setting of needlestick injuries or intentional release, restricting its use to "naturally acquired" infection could result in delay or deferral of therapy in these settings despite the demonstrated robust mortality benefit observed in naturally occurring infection and the potential for benefit in the context of needlestick exposure or other healthcare-associated exposures.

Clinical Virology Perspective

While Clinical Virology agrees that ansuvimab-zykl (Ebanga) should be approved based on the clinical results, the indication should state "naturally acquired" infection given that a needlestick exposure, which may occur at markedly higher concentrations of EBOV, was not studied and the EBOV disease course is likely to be significantly different in the event of an intentional release of EBOV.

Signatory Perspective

Although the current data are insufficient to demonstrate efficacy outside of "naturally acquired infection" (for example in the setting of a needlestick injury), I concur with the Clinical review team that restrictive labeling could lead to a delay in use and that depending on the nature of the exposure, ansuvimab-zykl (Ebanga) has the potential to mitigate disease and thereby offer benefit in combination with standard of care. Therefore, labeling that could delay or limit use in these settings will not be incorporated at this time based on the available data.

6.3.5. Use of an Inadequately Validated Bioanalytical Assay for Quantitation of Ansuvimab-zykl Concentrations in Serum of Healthy Humans

Issue

Use of an inadequately validated bioanalytical assay to measure serum concentrations of ansuvimab-zykl in the serum of healthy humans raised concerns about the reliability of the resulting PK data.

Background

Ansuvimab-zykl serum concentrations from Study 18-I-0069 were measured using an enzyme-linked immunosorbent assay developed and validated at the NIH's Vaccine Research Center (VRC). Notably, study samples were also analyzed at the VRC. Validation of the assay was based on a guidance ill-suited for the intended purpose. Specifically, the VRC relied upon the International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Uses quality guidance for validation of analytical procedures (ICH Q2 (R1)) instead

of the appropriate FDA or ICH guidance for bioanalytical method validation. As a result, important technical parameters required to establish assay validity such as accuracy, precision, quality controls, and duration of analyte stability were either omitted or insufficiently evaluated.

Assessment

While the Applicant's general assay validation report provides some insights into the suitability of the assay for its intended use, a formal sample analysis report detailing the assay's performance during bioanalysis of Study 18-I-0069 serum samples was not provided. The Applicant's explanation for this omission (Response to IR submitted September 14, 2020) notes that the VRC never developed a sample analysis report for submission. Instead, documentation of in-study assay performance was limited to: 1) a cumulative assay passing rate based on the total number of assay calibration curves which met a prespecified passing criterion and 2) acceptance of the performance of high- and low-quality control samples in each assay run based on unspecified criteria. Without a detailed sample analysis report, the reliability of data generated with this assay cannot be ascertained.

Conclusion

The information provided by the Applicant was insufficient to establish the assay's suitability for bioanalysis and the acceptability of the resulting PK data. Nonetheless, the ansuvimab-zykl PK profile suggested by the available data is consistent with that of other IgG1 monoclonal antibodies (mAb). Because PK data in this application does not inform efficacy, the review team agreed that this is strictly a labeling issue for Subsection 12.3 (Pharmacokinetics).

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The ansuvimab-zykl nonclinical safety studies included a good laboratory practice (GLP) 4-week, intravenous, repeat-dose toxicology study in rhesus monkeys, a GLP tissue cross-reactivity study in normal adult human tissues, and an assessment of polyspecificity and phospholipid binding. All pertinent studies and findings are summarized below. Full reviews for all studies are located in Section 13.1.

No adverse ansuvimab-zykl-related findings were observed in the GLP 4-week toxicology study in rhesus monkeys up to the highest dose tested (no-observed adverse effect level =500 mg/kg/dose). Further, no off-target binding was observed in the tissue cross-reactivity study with ansuvimab-zykl in normal human tissues, and no phospholipid binding was observed with ansuvimab-zykl in the in vitro assessment of polyspecificity. Genotoxicity, carcinogenicity, and reproductive toxicology studies have not been conducted with ansuvimab-zykl.

Overall, the nonclinical safety assessment for ansuvimab-zykl was considered acceptable to support licensing from a pharmacology/toxicology perspective. The exposure multiple at the no-observed adverse effect level for the GLP 4-week toxicology study in monkeys is presented in the following table (Table 20).

Table 20. Ansuvimab-zykl Exposure Multiples

Study	NOAEL (mg/kg/dose)	Adverse Findings	Nonclinical AUC (µg.day/mL)	Exposure Multiple[a]
4-week monkey	500	None	222,664[b]	7.6

Source: Review team analysis
[a] Based on mean steady-state exposures in healthy adult human subjects receiving a single 50 mg/kg IV infusion ($AUC_{0\text{-last}}$ =29288 µg.day/mL)
[b] Day 22 data
Abbreviations: AUC, area under the curve; NOAEL, no-observed-adverse-effect level

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

As with all therapeutic proteins, there is potential for immunogenicity. Treatment of patients with therapeutic protein products, such as monoclonal antibodies, may trigger immune responses of varying clinical relevance based on product- and patient-specific factors.

Because ansuvimab-zykl is a monoclonal antibody, it is capable of inducing antibody formation. Therefore, the formation of anti-drug antibodies (ADAs) against ansuvimab-zykl was measured in Study 18-I-0069. While no ADAs were detected in serum samples obtained following the administration of ansuvimab-zykl, two baseline serum samples tested positive in the screening assay. However, interpretation of these observations is limited by the incomplete validation of the ADA detection assay used in this study (see the OBP Immunogenicity Review by Dr. Davinna Ligons uploaded to Panorama on 12/16/2020).

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Ansuvimab-zykl has not been approved in any country; therefore, there has been no postmarketing experience with ansuvimab-zykl.

7.4. FDA Approach to the Safety Review

Adequacy of Applicant's Clinical Safety Assessments

Due to the challenges of data collection, the PALM Trial was designed with a reduced data collection plan. The sponsor of the trial, NIAID, noted in the protocol: "Every attempt will be made to document the nature [name/type] and the severity [grade per DAIDS toxicity table version 2.1, July 2017] of conditions present at baseline, particularly as pertains to the status of Ebola infection and vital organ function, so that meaningful data can be collected on the safety and efficacy impact of study interventions. It is acknowledged at the outset that this effort will likely be incomplete, and there may be unavoidable inconsistencies over time and from place to place, due to harsh conditions at treatment/study sites."

On Sunday February 24, 2019, there was an attack on the study team at the Katwa Ebola Treatment Centre, resulting in a fire. Various infrastructure and study supplies were destroyed. Another attack and fire occurred on Wednesday February 27, 2019 at the Butembo Ebola Treatment Centre, resulting in building destruction and major material damage. Some case report form (CRF) binders (paper copies) were lost during the fire; however, scanned copies of these

CRFs were retained. Médecins Sans Frontiéres, which was providing staffing for these facilities, withdrew their personnel after these events.

According to the 19-I-0003 PALM RCT protocol, study data collected at the bedside at study sites were to be later recorded as paper or electronic CRFs with subsequent transmission to the Data Coordinating Center. Data Coordinating Center personnel entered the data into an electronic database. Corrections to electronic data systems were to be tracked electronically (password protected and through an audit trail) with time, date, individual making the correction, and the nature of the change. Reports containing French terms were submitted to a certified vendor for authorized translation into English. In addition, any pertinent documentation (i.e., protocol and pharmacy manuals and informed consent forms) sent to the DRC by the NIAID was translated into French. Vital signs, signs and symptoms, optional procedures data, and supportive care were not queried. The chemistry laboratory data for the screening visit were reviewed and compared with source documents; however, no further information on the monitoring of chemistry laboratory data were provided.

After the final database review and inspections, NIAID allowed the sponsors of ansuvimab-zykl (Ridgeback) and REGN-EB3 (Regeneron) to submit queries. Although DAV requested that NIAID assure that data met Clinical Data Interchange Standards Consortium standards before sharing with Ridgeback and Regeneron, NIAID declined because NIAID was not directly responsible for submitting either BLA. After the database was locked, only the data from the ansuvimab-zykl and ZMapp arms were transferred to the Applicant for this BLA. Ridgeback then converted their respective datasets independently.

The Applicant submitted data from Study NIH-18-I-0069 (a Phase 1 healthy volunteer study) in support of the safety data from the PALM Trial. However, this study will not be considered essential to the assessment of safety for the proposed indication because only 10 volunteers received ansuvimab-zykl at the proposed dose. Additionally, the interaction of ansuvimab-zykl with the underlying EBOV infection was considered critical for the assessment of safety for the proposed treatment indication.

The initial BLA submission included data from the completed PALM RCT main phase and the ongoing MEURI EAP. No data were included for the PALM RCT extension phase (initiated August 10, 2019), which evaluated subjects randomized to receive either ansuvimab-zykl or REGN-EB3. Data from the PALM RCT covered enrollment through August 9, 2019 (database locked January 17, 2020), and data from the EAP covered outcomes as of September 20, 2019. From February 17 to April 3, 2020, no new cases of EBOV infection were reported in the DRC. However, on April 10, 2020, a new confirmed case was reported. The Applicant submitted a 60-day Safety Update Report on April 24, 2020, which covered corresponding interval data for each study until April 3, 2020. However, mortality data from the extension phase of the PALM RCT will not be shared with any third party until completion of the study.

Approach to Assessment of Clinical Trial Data

This review of clinical safety considers all of the challenges of data collection inherent with EBOV outbreaks and the sociopolitical challenges occurring in the location of the outbreak.

Because mortality was the primary efficacy endpoint of the PALM RCT, the assessments of benefit and risk overlap. With the demonstration of a statistically significant treatment effect on mortality, a degree of uncertainty with the assessment of safety can be accepted. Prespecified

testing was not proposed for any safety outcomes. Comparisons between treatment arms in the PALM Trial, however, are based on descriptive analyses. Pooling of the data from the PALM Trial with the EAP was not feasible due to significant differences in data collection (the EAP had incomplete and unstructured data reporting, lack of causality assessments, and challenges in obtaining follow up information).

Clinical trial data were independently analyzed using JMP and JReview software. Additional analyses were provided by the Clinical Data Scientist support team. All safety assessments and conclusions are those of the clinical review team unless otherwise specified.

7.5. Adequacy of Clinical Safety Database

Overall, the safety database is adequate to assess the safety of ansuvimab-zykl for the proposed indication, dosage regimen, and patient populations. Table 21 summarizes the clinical safety data available for evaluation.

Table 21. Overview of Clinical Safety Data

Study	Description	Number of Subjects
19-I-0003 (PALM RCT) (data cutoff 8/9/2019)	OL, RCT	Safety population: Ansuvimab-zykl =173, ZMapp =168 (post discharge follow-up of 58 days).
19-I-0003 (PALM Extension Phase) (data cutoff 4/3/2020)	OL, RCT	An estimated 180 have received ansuvimab-zykl (Assuming 1:1 randomization of 359 subjects. Safety reported only as SUSAR and pregnancies)
MEURI EAP (data cutoff 9/10/2019)	OL	N=251
NIH-18-I-0069	P1 FIH, HV	Ansuvimab-zykl =18 (N=10 at proposed dose), No placebo
Total ansuvimab-zykl safety database		**N=622**

Source: Reviewer's analysis
Abbreviations: FIH, first in human; HV, healthy volunteer; MEURI EAP, Monitored Emergency Use of Unregistered Interventions Expanded Access Protocol; N, number of subjects; OL, open-label; PALM, PAmoja TuLinde Maisha; RCT, randomized controlled trial; SUSAR, suspected unexpected serious adverse reaction

The PALM RCT and MEURI EAP differed in the methods used for the collection of safety information. The PALM RCT was randomized and systematically collected safety data from all treatment groups using CRFs. PALM also provided standard operating procedures to define serious adverse events (SAEs) as events not thought to be related to the underlying EBOV infection. Conversely, the MEURI EAP was not randomized, lacked a comparator treatment group, did not have criteria for SAEs specified in the protocol, and lacked verifiable investigators documented at the Ebola treatment units. The protocol did not specify safety data collection and the designated CRFs were not completed and returned to the Applicant. Additionally, the limited ability to communicate with the sites further diminished the capacity to collect information. Therefore, the safety data from MEURI EAP will not be integrated with the PALM RCT for this review. Instead, the PALM RCT is provided as the primary assessment of safety, and the MEURI EAP serves as supportive data. When available, supplemental analyses from MEURI EAP are provided in the following respective sections, where available.

In the PALM Trial, there was adequate assessment of exposure with ansuvimab-zykl, as ansuvimab-zykl was intended to be administered as a single infusion (whereas subjects in the ZMapp and remdesivir arms required multiple infusions). Exposure and treatment duration are summarized in Table 22.

Table 22. Duration of Exposure, Safety Population, PALM Trial

Number of Doses/Duration	Ansuvimab-zykl 50 mg/kg N=173	ZMapp N=168
Total number of doses administered	173	361
Infusions not administered completely	2 (1.1%)	13 (7.7%)
Any duration (including partial infusion)	173 (100%)	168 (100%)
≥2	0	104 (61.9%)
≥3	0	87 (51.7%)

Source: Applicant's 19-I-0003 post-text table 14.1.1.
Abbreviations: N, number of subjects; PALM, PAmoja TuLinde Maisha; RCT, randomized controlled trial

No SAEs in any subjects led to discontinuation. However, infusion of ansuvimab-zykl was discontinued in two subjects due to an adverse event (AE), while ZMapp infusion was discontinued in 13 subjects. In the two subjects who discontinued ansuvimab-zykl, one developed chills, dyspnea, fever, rigors/tremors, and tachypnea, while the other subject developed hypotension and tachypnea. Subjects infused with ZMapp also reported the following additional adverse reactions: vomiting, tachycardia, desaturation, diarrhea, agitation, dry cough, hypertension, anorexia, dyspepsia, headache, chest pain, oxygen desaturation, and convulsions. These could be due to the multiple infusions required to administer a full dose of ZMapp (3 x 50 mg/kg). As with SAEs, it is difficult to ascertain if these reactions were truly infusion-related or resulted due to *Zaire ebolavirus* infection.

Table 23 summarizes the duration of observation following receipt of study drug in the PALM RCT.

Table 23. Summary of Study Duration, Safety Population, PALM Trial

Parameter	Ansuvimab-zykl 50 mg/kg N=173	ZMapp N=168
Duration of observation period[a] (units)		
Mean (SD)	40.1 (26.0)	31.6 (27.7)
Median (min, max)	58.0 (1, 67)	48.5 (1, 66)
Duration of observation period, n (%)		
≥1 day	173 (100%)	168 (100%)
≥29 days	115 (66.4%)	85 (50.6%)
≥59 days	114 (65.9%)	84 (50.0%)

Source: Reviewer analysis and Applicant's 19-I-0003 Clinical Study Report Table 24 and post-text Table 14.1.1
[a] Duration of the observation period was defined as (death date or last known alive date − date of randomization) +1.
Abbreviations: N, number of subjects; n, number of subjects in subgroup; PALM, PAmoja TuLinde Maisha; RCT, randomized controlled trial; SD, standard deviation

In the MEURI EAP, from August 10, 2018 to September 10, 2019, a total of 251 subjects with laboratory confirmed *Zaire ebolavirus* infection received 50 mg/kg ansuvimab-zykl via a single IV infusion at four Ebola Treatment Centers (Alliance for International Medical Action, Médecins Sans Frontières, International Medical Corps, Samaritan's Purse, and World Health Organization/Ministry of Health) in one country (DRC). Subject disposition is summarized in Table 24.

Table 24. Summary of Disposition, Safety Population, MEURI EAP

Disposition	Ansuvimab-zykl N=251
All treated subjects	251 (100%)
Subjects who were discharged	170 (67.7%)
Subjects who died	81 (32.3%)

Source: Applicant's Clinical Study Report for MEURI EAP, Table 14.1.1 Data cutoff date September 20, 2019
Abbreviations: MEURI EAP, Monitored Emergency Use of Unregistered and Investigational Intervention expanded access protocol; N, number of subjects; n, number of subjects in subgroup

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

EBOV infection is associated with significant clinical manifestations and laboratory abnormalities that confound assessment of the safety of drugs administered to treat active disease. In subjects treated with ansuvimab-zykl, the observed safety profile was largely consistent with, or better than, the expected clinical presentation of EBOV infection.

7.6.1. Overall Adverse Event Summary

For the PALM Trial, only SAEs were recorded and summarized. The observation period was divided into three segments: pretreatment, treatment, and posttreatment. The pretreatment period was defined as the time elapsed from when the subjects gave informed consent and the start of the investigational product. The treatment period was defined as the time from the first dose of investigational product to 58 days after the last dose. The posttreatment period was defined as starting 58+1 days after the last dose of investigational product (after the on-treatment period). SAEs from each observation period were provided as data when available. Day 1 was the first day of the investigational product and day –1 was the day before; there was no Day 0.

Pretreatment SAEs were defined as SAEs that developed or worsened during the pretreatment period.

Treatment-emergent SAEs were defined as SAEs that developed or worsened during the on-treatment period.

Posttreatment SAEs were defined as SAEs that developed or worsened more than 58 days after the last dose of investigational product and were not considered drug related by the investigator.

The PALM RCT included the requirement that an event for a subject must be assessed as not related to their underlying EBOV infection or related to the study drug to be considered as an SAE. Further, when an SAE was identified, two assessments of relatedness to study medication were performed, one by the site investigator and the other by the pharmacovigilance working group.

The safety analysis population included all subjects who received either ZMapp or ansuvimab-zykl and were analyzed as treated (i.e., if a subject received the wrong treatment, they were analyzed as to their actual treatment assignment). The safety analysis population was used for all safety analyses. Subjects who first received ZMapp or remdesivir and who were subsequently switched to ansuvimab-zykl after August 9, 2019 based on DSMB recommendations are included in tables based on the drug received according to the initial randomization.

Table 25. Overview of Adverse Events, Safety Population, PALM Trial

Subjects Experiencing at Least One Event	Ansuvimab-zykl N=173	ZMapp N=168
Any nonserious adverse event[a]	66 (38.2%)	149 (88.7%)
Any SAE	11 (6.4%)	6 (3.6%)
SAEs with fatal outcome	1 (0.6%)	2 (1.2%)
SAE leading to discontinuation of study drug	0 (0%)	1 (0.6%)
SAE related to study drug	0 (0%)	2 (1.2%)

Source: Clinical Data Scientists analysis, and Applicant's 19-I-0003 Clinical Study Report Tables 20, 22 and 23, and post-text Table 16.2.3.1.
[a] Includes only events reported as adverse drug reactions that occurred during or on the day of infusion
Abbreviations: N, number of subjects in group; n, number of subjects with at least one event; PALM, PAmoja TuLinde Maisha; SAE, serious adverse event.

Infusion-Related Adverse Reactions

Infusion-related AEs were reported based on a checklist and included both prespecified and "other" AEs (Section 7.6.5) that occurred during infusion and included the full 24 hours of the treatment day. Fewer subjects (n=51; 29.5%) in the ansuvimab-zykl arm had prespecified infusion-related AEs as compared to subjects treated with ZMapp (n=142; 84.5%) (Table 26). The adverse reactions occurring in ≥5% of ansuvimab-zykl treated subjects included fever, tachycardia, hypotension, tachypnea, chills (rigors/tremors), diarrhea, and vomiting. The adverse reactions occurring in ≥5% of ZMapp treated subjects were the same as those seen with ansuvimab-zykl but also included hypoxia. The higher proportion of subjects with infusion adverse reactions in the ZMapp arm may be in part attributed to the 3 infusions that are required for administering a full dose of the drug (3 x 50 mg every third day) in these subjects.

Table 26. Prespecified Adverse Events, Safety Population, PALM Trial

Preferred Term	Ansuvimab-zykl N=173 n (%)	ZMapp N=168 n (%)	Risk Difference (95% CI)[1]
Any prespecified adverse reaction	51 (29.5)	142 (84.5)	-55 (-63.8, -46.3)
Pyrexia	30 (17.3)	97 (57.7)	-40.4 (-49.8, -31)
Chills	8 (4.6)	55 (32.7)	-28.1 (-35.9, -20.4)
Tachycardia	15 (8.7)	53 (31.5)	-22.8 (-31.1, -14.7)
Hypotension	13 (7.5)	52 (31)	-23.5 (-31.5, -15.4)
Tachypnoea	10 (5.8)	46 (27.4)	-21.6 (-29.2, -14)
Hypertension	2 (1.2)	17 (10.1)	-8.9 (-13.8, -4.1)
Dyspnoea	5 (2.9)	12 (7.1)	-4.2 (-8.9, 0.4)
Seizure	1 (0.6)	6 (3.6)	-3 (-6, 0)
Chest pain	0	6 (3.6)	-3.6 (-6.4, -0.8)
Rash	0	3 (1.8)	-1.8 (-3.8, 0.2)
Pruritus	0	2 (1.2)	-1.2 (-2.8, 0.4)
Oedema	0	1 (0.6)	-0.6 (-1.8, 0.6)
Flushing	0	1 (0.6)	-0.6 (-1.8, 0.6)

Source: Clinical Data Scientist analysis of adae.xpt; Software: R
Filter by AESCAT with "Prespecified"
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

Among *all* infusion-related AEs, which include both pre-specified infusion-related AEs during the first 24 hours after drug administration (Table 26) and the subsequent daily post-infusion AEs, are shown in Table 30. There were still fewer subjects (n=66; 38.2%) in the ansuvimab-

zykl arm who had infusion-related AEs as compared to subjects treated with ZMapp (n=149; 88.7%) (Table 27).

Table 27. Infusion-Related (Prespecified or Other) Adverse Events, Safety Population, PALM Trial

Preferred Term	Ansuvimab-zykl N=173 n (%)	ZMapp N=168 n (%)	Risk Difference (95% CI)[1]
Any prespecified or other adverse reaction	66 (38.2)	149 (88.7)	-50.5 (-59.2, -41.9)
Pyrexia	30 (17.3)	97 (57.7)	-40.4 (-49.8, -31)
Chills	8 (4.6)	55 (32.7)	-28.1 (-35.9, -20.4)
Tachycardia	15 (8.7)	53 (31.5)	-22.8 (-31.1, -14.7)
Hypotension	13 (7.5)	52 (31)	-23.5 (-31.5, -15.4)
Tachypnoea	10 (5.8)	47 (28)	-22.2 (-29.8, -14.6)
Vomiting	14 (8.1)	38 (22.6)	-14.5 (-22, -7)
Diarrhoea	15 (8.7)	31 (18.5)	-9.8 (-17, -2.6)
Oxygen saturation decreased	6 (3.5)	19 (11.3)	-7.8 (-13.4, -2.3)
Hypertension	2 (1.2)	17 (10.1)	-8.9 (-13.8, -4.1)
Dyspnoea	6 (3.5)	12 (7.1)	-3.6 (-8.4, 1.1)
Nausea	6 (3.5)	12 (7.1)	-3.6 (-8.4, 1.1)
Agitation	1 (0.6)	8 (4.8)	-4.2 (-7.6, -0.8)
Headache	3 (1.7)	8 (4.8)	-3.1 (-6.8, 0.7)
Chest pain	0	7 (4.2)	-4.2 (-7.2, -1.1)
Cough	1 (0.6)	6 (3.6)	-3 (-6, 0)
Decreased appetite	3 (1.7)	6 (3.6)	-1.9 (-5.3, 1.6)
Seizure	1 (0.6)	6 (3.6)	-3 (-6, 0)
Dizziness	3 (1.7)	5 (3)	-1.3 (-4.5, 2)
Abdominal pain	0	5 (3)	-3 (-5.5, -0.4)
Bradycardia	0	5 (3)	-3 (-5.5, -0.4)
Hiccups	2 (1.2)	4 (2.4)	-1.2 (-4, 1.6)
Malaise	0	4 (2.4)	-2.4 (-4.7, -0.1)
Abdominal pain upper	1 (0.6)	3 (1.8)	-1.2 (-3.5, 1.1)
Rash	0	3 (1.8)	-1.8 (-3.8, 0.2)
Hypothermia	1 (0.6)	2 (1.2)	-0.6 (-2.6, 1.4)
Pruritus	0	2 (1.2)	-1.2 (-2.8, 0.4)
Haematemesis	1 (0.6)	1 (0.6)	0 (-1.6, 1.6)
Abdominal distension	0	1 (0.6)	-0.6 (-1.8, 0.6)
Epistaxis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Eye pain	0	1 (0.6)	-0.6 (-1.8, 0.6)
Back pain	0	1 (0.6)	-0.6 (-1.8, 0.6)
Dysphagia	0	1 (0.6)	-0.6 (-1.8, 0.6)
Nasal flaring	0	1 (0.6)	-0.6 (-1.8, 0.6)
Palpitations	0	1 (0.6)	-0.6 (-1.8, 0.6)
Dyspepsia	0	1 (0.6)	-0.6 (-1.8, 0.6)
Feeling hot	0	1 (0.6)	-0.6 (-1.8, 0.6)
Flushing	0	1 (0.6)	-0.6 (-1.8, 0.6)
Oedema	0	1 (0.6)	-0.6 (-1.8, 0.6)
Melaena	0	1 (0.6)	-0.6 (-1.8, 0.6)
Haemorrhage	1 (0.6)	0	0.6 (-0.6, 1.7)

Source: Clinical Data Scientist analysis of adae.xpt; Software: R
Filter by AESCAT with "Prespecified" and "Other Reactions"
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

Clinical Symptoms Monitored for Drug Toxicity

On each study day while in the ETU and on Day 28 and Day 58, the current symptoms presented by each subject were collected to guide the physician in conducting a consistent exam and history throughout the subject's stay in the ETU. The list of targeted symptoms included: fever, cough, mental state change, hearing loss, vision loss, headache, vomiting, diarrhea, abdominal pain, shortness of breath, hiccups, rash, edema, conjunctival injection, convulsions, and hemorrhage. The proportion of subjects with at least one clinical symptom starting or reappearing after Day 28 through Day 58 are presented by treatment arms in Table 28.

One hundred sixty-eight (97%) subjects in the ansuvimab-zykl arm and 167 (99%) subjects in the ZMapp arm had clinical symptoms on Day 1. These symptoms were reduced to 38/115 (33%) and 38/114 (33%) subjects on Days 28 and 58, respectively, in the ansuvimab-zykl arm. In the ZMapp arm, 32/85 (38%) subjects had clinical symptoms on Day 28, which was reduced to 19/84 (23%) subjects on Day 58. Although, by Day 58, clinical symptoms appeared to be lower in the ZMapp-treated subjects, there were fewer alive subjects on Day 58 in comparison to ansuvimab-zykl-treated subjects.

Table 28. Overview of Subjects With Clinical Symptoms at Day 1, Day 28 and Day 58, Safety Population, PALM Trial

Parameter	Ansuvimab-zykl 50 mg/kg N=173	ZMapp N=168
Subjects with a clinical symptom at, n/N (%)		
Day 1	168/173 (97.1%)	167/168 (99.4%)
Day 28	38/115 (33.0%)	32/85 (37.6%)
Day 58	38/114 (33.3%)	19/84 (22.6%)

Source: Applicant's 19-I-0003 Clinical Study Report Table 24.
Abbreviations: N, number of subjects; n, number of subjects in subgroup; PALM, PAmoja TuLinde Maisha; RCT, randomized controlled trial.

Clinical symptoms did not differ significantly between the two arms and are likely to be due to the underlying EBOV infection. In conclusion, there was no observed evidence of ansuvimab-zykl-related drug toxicity based on follow-up of clinical symptoms through Day 58.

7.6.2. Deaths

Deaths are discussed in Section 6.2.4 as a primary efficacy endpoint. One SAE of malnutrition that resulted in death occurred in the ansuvimab-zykl arm 45 days after drug administration. Subject (b) (6) was a female neonate born on (b) (6), via C-section. Her mother died from *Zaire ebolavirus* infection the same day. The neonate was treated after birth and discharged on (b) (6) after recovering. She returned on (b) (6) for her Day 28 visit and there were no concerns. On (b) (6) she presented with dyspnea to the TUMAINI health facility. However, no treatment was administered. On (b) (6), she was transferred to Beni General Hospital but while en route she experienced cardio-respiratory arrest and died. The death was attributed to severe malnutrition by the attendant physician. This reviewer agrees with the investigator's and Applicant's assessments that this fatal SAE was not related to ansuvimab-zykl.

Additional details regarding all deaths that occurred in the study are presented in Section 17.

7.6.3. Serious Adverse Events

SAEs are summarized in Table 29. None of the 11 SAEs that occurred in the ansuvimab-zykl arm were considered related to the drug, and some of them, such as neurologic and psychiatric symptoms, may have been confounded by the underlying EBOV infection. Additional details regarding AEs by system organ class and preferred term are presented in Section 17.

Table 29. Serious Adverse Events, Safety Population, PALM Trial

Actual Arm	Unique Subj ID	SAE Start Day	SAE End Day	SAE Duration (Days)	Preferred Term	Outcome
Ansuvimab-zykl	(b) (6)	2	23	22	Stevens-Johnson syndrome	Recovered/resolved
		44	45	2	Malnutrition	Death
		40	48	9	Cerebral Malaria	Recovered/resolved
		28	-	-	Psychosis	Not recovered/ not resolved by Day 58 follow-up
		10	-	-	Behavior disorder	Not recovered/ not resolved by Day 58 follow-up
		6	-	-	Blind right eye	Not recovered/ not resolved by Day 58 follow-up
		34	74	41	Edema lower limb	Recovered/resolved
		15	60	46	Pressure ulcer	Recovered/resolved
		54	56	3	Fetal death in utero	Recovered/resolved
		16	25	10	Behavior disorder	Recovered/resolved
		28	40	13	Dyspepsia	Recovered/resolved
ZMapp		1	2	2	Diarrhea	Fatal
		1	2	2	Vomiting	Fatal
		157	-	-	Hydrocephaly	Not recovered/ not resolved by Day 58 follow-up
		157	-	-	Umbilical cord short	Not recovered/ not resolved by Day 58 follow-up
		1	2	2	Anaphylactic shock	Fatal
		96	-	-	Fetal death in utero	Not recovered/not resolved
		14	27	14	Edema lower limb	Recovered/resolved with sequelae
		2	74	73	Urethral injury	Recovered/resolved

Source: Applicant 19-I-0003 Clinical Study Report post-text table 16.2.3.1
Coded as MedDRA preferred terms
Abbreviations: PALM, PAmoja TuLinde Maisha; SAE, serious adverse event

In the ansuvimab-zykl arm, 11 subjects had SAEs and only one was fatal (Subject (b) (6)) (see Section 7.6.2). Subject narratives for the other ten SAEs are provided below.

Subject (b) (6) was a 5-year-old female who had a generalized rash on (b) (6) which led to a prolonged hospitalization. Subject (b) (6) was initially diagnosed and hospitalized in Beni Ebola Treatment Unit on (b) (6) with *Zaire ebolavirus* infection. The subject was enrolled, randomized, and dosed on (b) (6) and received 800 mg of ansuvimab-zykl via IV infusion as per protocol. The subject had no skin lesions before hospitalization. In

addition to the single dose of ansuvimab-zykl, she received the following treatment, among others: cefixime (b) (6) albendazole (b) (6) ceftriaxone (b) (6) coartem (b) (6) The subject had pruritic skin lesions that started and regressed on (b) (6) with promethazine. On (b) (6) she presented with disseminated papular rash, generalized pruritus, eye secretions, bulbar conjunctiva injections, and mouth ulcers. She was discharged from ETU and transferred to Beni General Hospital on (b) (6). Her hospitalization was extended at the Beni General Hospital and she was discharged on (b) (6), after resolution of the rash.

The study investigators were made aware of the event on April 2, 2019 and reported the event as an SAE due to the prolonged hospitalization and judged the event to not be related to study drug. The Medical Monitors assessed the relationship to the study drug as not related and concluded that subject probably had Stevens Johnson syndrome due to hypersensitivity (cross allergy) to cephalosporins (cefixime and ceftriaxone). This SAE was considered resolved.

Subject (b) (6) was a 10-month-old male patient who developed an SAE of cerebral malaria, after recovering from *Zaire ebolavirus* infection. He was admitted and randomized on (b) (6) and discharged from the ETU on (b) (6) after two negative PCR tests. He attended the Day 28 visit on (b) (6) without issue. On (b) (6), he was brought to a health facility with a complaint of loss of consciousness and fever. A blood sample was collected for lab tests, and he was diagnosed with cerebral malaria. He was treated with ceftriaxone, gentamicin, ciprofloxacin, artesunate injection, and paracetamol. He recovered, and the SAE was considered resolved.

Subject (b) (6) was a 28-year-old male patient who was admitted and randomized on (b) (6) with a positive PCR result, fever, conjunctival injection, and epigastric pain. He had a history of gastritis, was not vaccinated, and had a known contact. The date of EBOV symptom onset was (b) (6). He was treated with paracetamol, ceftriaxone, multivitamin, intravenous Ringer's lactate and saline solution, and omeprazole. Between (b) (6), he had myalgia, pruritus, and joint pain and recovered from EBOV. However, after discharge on (b) (6) he was referred to a psychiatric facility on (b) (6) for probable hallucinatory psychosis post-healing, and follow-up was made by phone on Day 28 and Day 58. During hospitalization, the patient developed the following psychiatric disorders: hyper-vigilance, insomnia due to fear of being slaughtered, visual hallucination, and psycho-motor hallucination. As of the last day of follow-up, this SAE was not resolved. It was determined to be not related to ansuvimab-zykl.

Subject (b) (6) was a 17-year-old female who developed a behavior disorder 10 days after admission. Her EBOV symptoms started on (b) (6). She was admitted on (b) (6) with a positive PCR result and she was randomized and treated with ansuvimab-zykl on the same date. There was no adverse reaction to the drug. The onset of the SAE was on (b) (6), when she attacked one of the patients hospitalized in the convalescent area. She said she will kill them all and took an item to threaten the others. Given this threat, Largactil was administered but was not effective. On (b) (6), a neuropsychiatric consultation was conducted, and the patient was treated with haldol and artane. The crisis abated but re-occurred. On (b) (6), the prescription was changed, a reference to a specialized center was requested, and tranxene 10 mg was prescribed. On (b) (6), she was discharged and referred to case management, leading to hospitalization. The SAE was determined to be not related to ansuvimab-zykl and was considered not resolved/not recovered by the end of follow-up.

Subject (b) (6) was a 29-year-old female patient with no relevant medical history who presented with an SAE of right eye blindness. Her date of EBOV symptom onset was on (b) (6), and she was admitted on (b) (6). She was enrolled, randomized, and treated on (b) (6). On admission she had fever, conjunctival injection, gum bleeding, and coma. There was no infusion reaction and there was a good virologic and clinical evolution. The patient had eye pain by the time she was discharged on (b) (6). At home, this eye pain increased on (b) (6) and she consulted an ophthalmologist for persisting pain, tearing, and vision loss. The patient is currently followed up by an ophthalmologist for right eye blindness. The SAE was considered not related to ansuvimab-zykl and was not resolved by the end of follow-up.

Subject (b) (6) was a 22-year-old male who was a basketball player and who reported an SAE of lower leg edema. His EBOV symptom onset was on (b) (6). He was admitted, enrolled, randomized, and treated on (b) (6). On admission he had a positive PCR result, cough, headache, diarrhea, vomiting, and asthenia. After treatment he had good clinical and virologic resolution and he was discharged on (b) (6). Two days later, he played basketball and on the evening of (b) (6), he developed lower limb edema, which persisted with pain, then limitation of motion where he was unable to walk on (b) (6). He checked into a facility where he was treated with tribexfort and paracetamol. His SAE resolved and he resumed his activities. This SAE was determined to be not related to the study drug.

Subject (b) (6) was a 36-year-old male with no relevant medical history who developed an SAE of pressure ulcer. He was admitted, enrolled, randomized, and treated on (b) (6) with a positive PCR result. On admission he had vomiting, diarrhea, asthenia, dyspnea, hiccup, melena, and hematemesis. He developed hypothermia during the infusion of ansuvimab-zykl. On (b) (6) he developed diarrhea, asthenia, lower limb edema, clouded mind, consciousness disorder, anemia, injection site bleeding, hiccup, and occurrence of a bedsore. His PCR results were negative on (b) (6) but his hospitalization was prolonged to (b) (6), justifying his transfer to another health facility for better management of bedsores. This SAE was not related to the study drug.

Subject (b) (6) was a 34-year-old female with no relevant medical history who had an SAE of in-utero fetal death. She was pregnant on admission with a last menstrual period on (b) (6). She was admitted and randomized on (b) (6) and received ansuvimab-zykl. On (b) (6), she presented with lack of fetal movements as well as hypogastric and low back pain at a gestational age of 22 weeks. She consulted at the ETU where, on (b) (6), she delivered a fetus with first degree maceration and no external visible malformation. She was treated with amoxicillin, metronidazole, and oxytocin. Post-abortion she recovered well. This SAE was considered not related to ansuvimab-zykl and was considered resolved.

Subject (b) (6) was a 31-year-old female with a history of behavior disorder who reported an SAE of behavior disorder. She was admitted and randomized for treatment on (b) (6) On (b) (6) she developed an SAE of behavior disorder with logorrhea, euphoria, and psycho-motor agitation. She was given a sedative and after discharge was followed up as an inpatient at Graben University Hospital, where she was treated with paracetamol, largactil, and diazepam. She was released and considered stable on (b) (6) after resolution of her symptoms. This SAE was determined to be not related to ansuvimab-zykl and was considered resolved.

Subject (b) (6) was a 51-year-old female with no relevant medical history who reported an SAE of dyspepsia. She was admitted and randomized on (b) (6) On admission she had

arthralgia and anorexia. During her stay she presented with fever, diarrhea, abdominal pain, and asthenia, and was treated with intravenous fluid, paracetamol, ceftriaxone, and omeprazole. She was discharged from the ETU on (b) (6). On (b) (6) she presented with epigastralgia (dyspepsia) and palpitations, which led her to return to the ETU (Médecins Sans Frontiéres), where she was treated for 3 days. Her SAE resolved and was determined to be not related to ansuvimab-zykl.

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

Two subjects (1.1%) in the ansuvimab-zykl arm of the PALM RCT did not receive their complete infusion because of issues that occurred during infusion. The first subject was Subject (b) (6) who was a 40-year-old male who experienced prespecified infusion-related AEs of chills (rigors/tremors), difficulty breathing, tachypnea, and fever. The drug was discontinued, and the subject received intravenous fluids and supportive care. However, he did not survive and died on Day 2 from complications of *Zaire ebolavirus* infection. The second patient was Subject (b) (6), a 20-year-old female who experienced prespecified infusion-related AEs of hypotension and tachypnea. The drug was discontinued, and over the subsequent days, she received intravenous fluids and supportive therapy until she died on Day 8 from complications of *Zaire ebolavirus* infection.

Additional details regarding AEs that led to discontinuations by system organ class and preferred term are presented in Section 17.

In the MEURI EAP, no information regarding treatment discontinuations was provided by the Applicant.

7.6.5. Treatment-Emergent Adverse Events

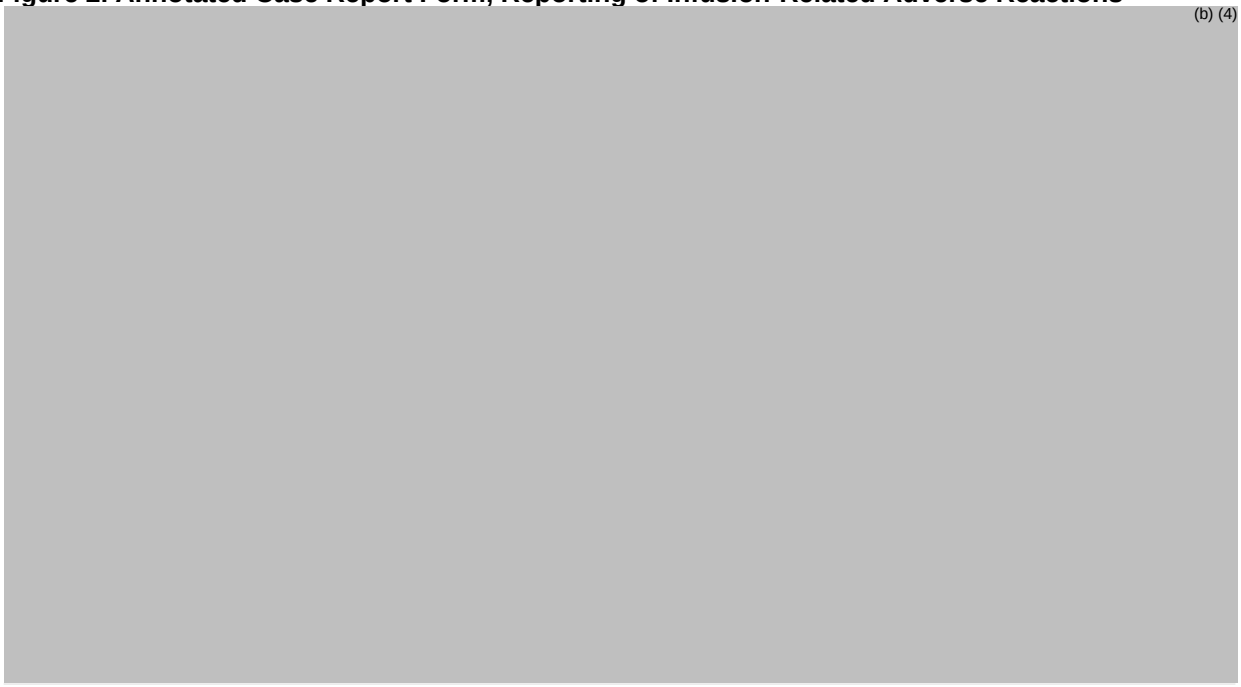
The Applicant submitted data from two studies: a Phase 1 first-in-human, healthy volunteer study (VRC 608/NIH-18-I-0069); and an open-label randomized clinical trial (PALM Trial).

The first study was a Phase 1, open-label, dose escalation study (5 mg/kg, 25 mg/kg, 50 IV without a placebo group), to investigate the safety, tolerability, immunogenicity, and PK of ansuvimab-zykl in 18 healthy adults. Only ten subjects (Group 3) received the full proposed dose of 50 mg/kg. In this small subset, there were few reported treatment-emergent adverse events. Systemic adverse events in 4/18 (22%) were all mild and resolved within 1 to 4 days (malaise, myalgia, headache, chills, nausea, and joint pain). There were no unsolicited AEs, one unrelated SAE (hospitalization for vomiting and syncope 84 days after administration), and no deaths. Although Study VRC 608/NIH-18-I-0069 was not confounded by underlying EBOV infection, the sample size was too small to make an adequate assessment of the safety of ansuvimab-zykl. The study population (only healthy men and women, 18 to 60 years of age) was also inadequate to accurately describe the clinical safety outcomes in EBOV-infected patients.

The main safety data considered in this review were those reported in the PALM RCT where signs and symptoms were assessed in the presence of EBOV infection. While underlying EBOV infection may have confounded the assessment of signs and symptoms and the relationship to the study drug, the PALM safety data still provide a more accurate representation of the anticipated safety outcomes in a real-life EBOV outbreak with infected patients.

In the PALM RCT, TEAEs were collected in the CRF in the form of a checklist of prespecified infusion-related AEs (Figure 2).

Figure 2. Annotated Case Report Form, Reporting of Infusion-Related Adverse Reactions



Source: From Annotated Case Report form provided by Applicant

Table 30 summarizes infusion-related AEs based on the reports in the CRF, as described above, as well as terms used in the narratives (the check box for "Other, specify"). However, it should be noted that terms from the narratives were not reported consistently because they were not specifically intended to capture infusion reactions. Narratives were provided only for subjects who died and often did not include associated information, such as assessment of their relationship to the study drug infusion. Because there were more deaths in the ZMapp arm, there were more narratives for the ZMapp arm than the ansuvimab-zykl arm.

The inclusion or exclusion of the terms that were not prespecified infusion reactions did not significantly impact the profile of the most common events (occurring in ≥10% of subjects in the PALM Trial): pyrexia (or "elevation of fever" as prespecified in the CRF), tachycardia, diarrhea, vomiting, hypotension, tachypnea, chills (common MedDRA term for both "chills" and "rigors/tremors"), and hypoxia.

Table 30. Infusion-Related (Prespecified in First 24 Hours or After the First Day) Adverse Events With Incidence of ≥1% in the Ansuvimab-zykl Arm, Safety Population, PALM Trial

Adverse Event[a]	Ansuvimab-zykl N=173 n (%)	ZMapp[c] N=168 n (%)
Any prespecified or other adverse reaction	66 (38.2)	149 (88.7)
Pyrexia[b]	30 (17.3)	97 (57.7)
Tachycardia[b]	15 (8.7)	53 (31.5)
Diarrhea	15 (8.7)	31 (18.4)
Vomiting	14 (8.1)	38 (22.6)
Hypotension[b]	13 (7.5)	52 (31)
Tachypnea[b]	10 (5.8)	47 (28)
Chills[b]	8 (4.6)	55 (32.7)
Dyspnea[b]	6 (3.5)	12 (7.1)
Nausea	6 (3.5)	12 (7.1)
Hypoxia	6 (3.4)	19 (11.3)
Headache	3 (1.7)	8 (4.8)
Decreased appetite	3 (1.7)	6 (3.6)
Dizziness	3 (1.7)	5 (3)
Hypertension[b]	2 (1.2)	17 (10.1)
Hiccups	2 (1.2)	4 (2.4)

Source: Clinical Data Scientist analysis of adae.xpt; Software: R
Filter by AESCAT with "Prespecified" and "Other Reactions"
[a] Adverse events in this table were reported as preferred terms from a list of predefined or other adverse events that occurred reported on the day of infusion and included signs and symptoms that occurred during or immediately after infusion. These terms were reported in the CRF. The MedDRA (version 22.1) coding dictionary was used.
[b] Adverse events that were prespecified. Note that "elevation in fever" mapped to the MedDRA term "pyrexia."
[c] Adverse events were reported on the day of infusion, ZMapp was to be administered as three separate infusions on up to three separate days.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; PALM, PAmoja TuLinde Maisha

Additional signs and symptoms were also reported on a daily basis while subjects were in the ETU. The following prespecified symptoms were collected: fever, cough, mental state change, hearing loss, vision loss, headache, vomiting, diarrhea, abdominal pain, shortness of breath/difficulty breathing, hiccups, rash, edema, conjunctival injection, convulsions, and hemorrhage (Figure 3). Other symptoms reported by the investigator were also included as a separate category under "other current symptoms." Presentation of these findings helped to describe safety findings beyond the immediate adverse reactions reported on the day(s) of infusion. Prespecified symptoms, however, were meant to closely follow resolution of the infection; therefore, the ability to assess the relationship of these symptoms to the study drug as "adverse drug reactions" is limited.

Figure 3. Annotated Case Report Form, Reporting of Daily Follow-Up of Symptoms

Source: From Annotated Case Report form provided by Applicant

Table 31 summarizes the prespecified symptoms experienced postbaseline. There was some uncertainty with this analysis, however, due to inconsistencies found in the data when compared with the NIH datasets submitted to IND-125530. The discrepancies were not clinically significant, but an audit of the data suggested that there may have been errors in translating data that impacted the analysis study dates associated with some symptoms. Estimates of the incidence for the most common symptoms (diarrhea, fever, and vomiting) were satisfactory to include in labeling as occurring in at least 40% of subjects in the days following infusion. However, given possible errors in transposition of study dates, the exact percentage for the most common symptoms were not included in labeling.

Table 31. Prespecified Symptoms Experienced Postbaseline, Safety Population, PALM Trial

Preferred Term	Ansuvimab-zykl N=173 n (%)	ZMapp N=168 n (%)
Diarrhea	112 (64.7)	118 (70.2)
Fever	110 (63.6)	88 (52.4)
Abdominal pain	91 (52.6)	85 (50.6)
Vomiting	77 (44.5)	85 (50.6)
Headache	67 (38.7)	61 (36.3)
Shortness of breath/difficult breathing	41 (23.7)	56 (33.3)
Conjunctival injection	39 (22.5)	52 (31)
Hemorrhage	38 (22)	44 (26.2)
Edema	39 (22.5)	43 (25.6)
Other symptoms: physical asthenia	48 (27.7)	42 (25)
Cough	30 (17.3)	40 (23.8)
Change in mental state	26 (15)	38 (22.6)
Other symptoms: asthenia	26 (15)	31 (18.5)
Rash	8 (4.6)	17 (10.1)
Convulsions	11 (6.4)	15 (8.9)

Source: Clinical Data Scientist analysis of adce.xpt; Software: R
Filter CECAT with “Current Symptoms”
Exclude “Day 1”
Symptoms were reported on a daily basis covering the prior 24-hour period.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; PALM, PAmoja TuLinde Maisha

In conclusion, postbaseline (postdosing) symptoms did not differ significantly between the two arms and are likely to be due to the underlying EBOV infection.

7.6.6. Laboratory Findings

Laboratory evaluations for creatinine, potassium, sodium, AST, and ALT were taken at each inpatient study day. Additional post-treatment laboratory evaluations were optional and included (but not limited to) a complete blood count with differential, metabolic panel, hepatic panel, urinalysis test, and pregnancy test.

These laboratory data were collected in the PALM Trial in adult and pediatric subjects. Table 32 summarizes changes limited to worsening grade (using DAIDS criteria) following treatment with ansuvimab-zykl. Laboratory tests are also reflective of the underlying illness being treated; therefore, the assessment of abnormalities is also highly confounded.

Nevertheless, comparisons between the ansuvimab-zykl and ZMapp arms did not reveal significant differences in postbaseline laboratory abnormalities caused by either study drug. The laboratory abnormalities observed are clinically expected in *Zaire ebolavirus* infection and, in those who survived, generally improved over time as subjects resolved their illness.

Table 32. Adult and Pediatric Subjects Meeting Laboratory Abnormality Criteria, Cumulative Worsened Grade From Baseline, Safety Population, PALM Trial

Laboratory Test	Ansuvimab-zykl N=173 n (%)	ZMapp N=168 n (%)
Sodium (mmol/L) increased		
Grade 3 or 4 (≥154 mmol/L)	9 (5.2)	7 (4.2)
Sodium (mmol/L) decreased		
Grade 3 or 4 (<125 mmol/L)	13 (7.5)	19 (11.3)
Potassium (mmol/L) increased		
Grade 3 or 4 (≥6.5 mmol/L)	25 (14.5)	20 (11.9)
Potassium (mmol/L) decreased		
Grade 3 or 4 (<2.5 mmol/L)	11 (6.4)	13 (7.7)
Creatinine (mg/dL) increased		
Grade 3 or 4 (>1.8x ULN or increase to ≥1.5x baseline)	46 (26.6)	38 (22.6)
Alanine aminotransferase (U/L) increased		
Grade 3 or 4 (≥5x ULN)	20 (11.6)	23 (13.7)
Aspartate aminotransferase (U/L) increased		
Grade 3 or 4 (≥5x ULN)	23 (13.3)	30 (17.9)

Source: Clinical Data Scientist analysis of adlb.xpt, Software: R
Grading scale used was DAIDS corrected version 2.1.
[a] ULN for serum creatinine =1.2 mg/dL; ULN for alanine aminotransferase =47 U/L; ULN for aspartate aminotransferase =38 U/L.
Abbreviations: N, number of subjects with relevant laboratory data; n, number of subjects with abnormality; PALM, PAmoja TuLinde Maisha; ULN, upper limit of normal

Additional analyses of laboratory data from the PALM RCT are presented in Section 17. However, clinical laboratory data were not systematically collected in the MEURI EAP.

7.6.7. Vital Signs

Vital sign measurements were taken at baseline, each inpatient study day, and at Day 28 and Day 58. Measurements included weight, blood pressure, pulse, body temperature, respiratory rate, and oxygen saturation.

There was no clinically significant difference in vital signs between ansuvimab-zykl-treated and control-treated subjects at the different observed time points. The observed changes were likely due to the underlying EBOV infection. However, the number of subjects by Day 58 were much lower in the control arm compared to the ansuvimab-zykl arm due to the greater proportion of deaths in the control arm. Additional details of vital signs are provided in selected boxplots in Section 17 for Day 1, Day 28, Day 58, and final assessment by treatment group.

7.7. Key Review Issues Relevant to Evaluation of Risk

Review issues relevant to the evaluation of risk include:

- Risks associated with endotoxin levels for the proposed total infusion volumes and infusion times for pediatrics, and administration issues in neonates.
- The development of resistance against ansuvimab-zykl has not been adequately characterized.
- Potential risks of immunogenicity.

7.7.1. Risks Associated With Endotoxin Levels for the Proposed Total Infusion Volumes for Pediatrics, and Administration Issues in Neonates

Issue

The proposed Dosage and Administration section of the label instructed users to dilute Ebanga in 0.9% sodium chloride or lactated Ringer's for injection (b) (4) Potential risks include endotoxin levels exceeding the recommended limit when Ebanga is combined with large volumes of diluents and volume overload in low-birth-weight infants.

Background

The primary review division (DAV) placed an interoffice neonatal-perinatal medicine consultation request to the Office of Pediatric Therapeutics (OPT). In the responding memorandum, Gerri Baer, MD, Supervisory Medical Officer for the Pharmacovigilance and Neonatology Team, noted that for preterm neonates, especially those less than 2 kg birth weight, clinicians must pay close attention to fluid and electrolyte balance to avoid generalized edema/anasarca, pulmonary edema, patent ductus arteriosus, chronic lung disease of prematurity, and intraventricular hemorrhage. In addition, glomerular filtration rate is low at birth and increases over the first year of life, with otherwise healthy preterm neonates having a glomerular filtration rate as low as 10-20 mL/min/1.73m^2 at birth (Kastl 2017) Neonates cannot easily dispose of excess fluid in the setting of prematurity, critical illness and inflammation. The daily fluid intake for extremely preterm neonates is typically maintained from 140 – 180 mL/kg day, with higher fluid intakes needed at times for neonates with significant insensible losses. Especially in the first several days of life, for example, a 0.5 kg neonate may require up to 200 mL/kg/day.

Note that the recommendations fromthe memorandum by OPT are also reflected in the assessment and conclusions of this section.

Assessment

The Sponsor's original proposed labeling (b) (4) Based on the initial clinical experience using the desired 60-minute infusion time, the Applicant proposed (b) (4) Given that the USP endotoxin unit (EU) limit for ansuvimab-zykl is (b) (4) for 0.9% sodium chloride injection, the total potential endotoxin input for the infusion solution administered over 60 minutes would exceed the threshold pyrogenic dose of (b) (4) EU/kg/hour for patients with body weight ≤16 kg. For example, a pediatric patient of 10 kg would be (b) (4) EU/kg/hour) from the saline alone (Table 33). Combined with the drug, the infusion solution would exceed the limit ((b) (4) EU/kg/hour).

Table 33. Theoretical Infusion Volumes of Ansuvimab-zykl for Patients Weighing 10 kg or Higher Administered Over One Hour

Patient Weight	Endotoxin From Diluent[a]	Endotoxin From Ansuvimab-zykl[b]	Total Endotoxin[c]
10 kg	(b) (4) EU	(b) (4) EU	(b) (4) EU/kg/hour
20 kg		EU	EU/kg/hour
30 kg		EU	EU/kg/hour
40 kg		EU	EU/kg/hour
50 kg		EU	EU/kg/hour
60 kg		EU	EU/kg/hour
70 kg		EU	EU/kg/hour
80 kg		EU	EU/kg/hour
90 kg		EU	EU/kg/hour
100 kg		EU	EU/kg/hour

Source: Table created by Office of Pharmaceutical Manufacturing Assessment (OPMA), OPQ, CMC.
[a] Endotoxin unit limit from diluent calculated using (b) (4)
[b] Endotoxin limit from ansuvimab-zykl calculated using (b) (4)
[c] (b) (4)
Abbreviations: EU, endotoxin unit

To ensure that the threshold pyrogenic dose of (b) (4) EU/kg/hour would not be exceeded in children and infants with lower weights, a longer infusion time or smaller infusion volume would be needed based on the patient's weight. For ansuvimab-zykl, it was reasonable to reduce the volume of diluent to that which would still allow the final concentration of the diluted solution to remain within acceptable limits (between 8 to 30 mg/mL) and allow the infusion to be administered over 60 minutes. Table 34 was proposed to the Applicant to address this concern.

Table 34. Proposed Theoretical Infusion Volumes of Ansuvimab-zykl for Patients Weighing 0.5 kg or Higher Administered Over One Hour

BW (kg)	Volume of Ansuvimab-zykl	Diluent Volume (Protein Concentration)	Total Endotoxin at Specification of (b) (4)
0.5 to <1	1 mL per kg of BW[a]	2.5 mL (10-20 mg/mL)	
1 to 1.9		5 mL (10-20 mg/mL)	
2 to 10		10 mL (10-50 mg/mL)	
11 to 25		25 mL (25-50 mg/mL)	
26 to 50		50 mL (25-50 mg/mL)	
51 to 100		100 mL (25-50 mg/mL)	
100 to 150		150 mL (33-50 mg/mL)	

Source: Table created by Office of Pharmaceutical Manufacturing Assessment (OPMA), OPQ, CMC.
[a] The dose is 50 mg of ansuvimab-zykl per kg of body weight
Abbreviation: BW, body weight

The Applicant agreed to these revised diluent volumes for patients with low weights, and revised the original labeling to include separate recommendations for administration to neonates and infants from 0.5 kg – (b) (4); and provided instructions to use a syringe pump for patients weighing 0.5 to (b) (4) which was considered satisfactory by the review team.

Another issue of concern was the Applicant's proposed labeling instructions (b) (4) and after labeling discussions, the Applicant agreed with the following revised language.

"At the end of the infusion, if a syringe pump was used, then remove the syringe and flush with 2 to 5 ml of diluent, but not to exceed the total infusion volume. If an infusion bag was used,

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

The following modifications (Table 35) satisfied the concerns about fluid administration volume and diluent flush in patients weighing <2 kg and were added to the label under "Dilution Instructions" in Section "2.2. Preparation, Administration, and Storage Instructions."

Table 35. Ebanga Volume, Diluent Volume, and Total Infusion Volume by Body Weight

Body Weight	Volume of Ebanga	Diluent Volume[a,b]	Final Infusion Volume	Syringe or Infusion Bag Volume for IV Administration
0.5 kg	1 mL/kg	2.5 mL	3 mL	10 mL syringe compatible with
1 kg		5 mL	6 mL	IV infusion pump
2 to 10 kg		10 mL	12 to 20 mL	25 mL IV bag
11 to 25 kg		25 mL	36 to 50 mL	50 mL IV bag
26 to 50 kg		50 mL	76 to 100 mL	100 mL IV bag
51 to 100 kg		100 mL	151 to 200 mL	250 mL IV bag
101 kg and above		150 mL	≥251 mL	500 mL IV bag

Source: Table 1. From Label in Section 2.2 under Dilution Instructions.
[a] The recommended diluent volume ensures the final concentration of the diluted solution is approximately 8 to 30 mg/mL.
[b] For IV bag administration, the diluent volume column includes the volume of diluent needed to remain in the infusion bag.

The diluents recommended in labeling are either 0.9% sodium chloride injection or lactated Ringers injection. For neonates, neither is optimal, but since there are no available compatibility data to allow use of 5% dextrose as a diluent for ansuvimab-zykl administration; therefore, the labeling will only include use of normal saline, USP, and lactated Ringer's injection, USP, as diluent for both pediatric and adult patients.

Because no drug compatibility testing was performed, the following statement was added to the label: "Do not co-administer other drugs simultaneously through the same infusion line."

However, it is recognized that multiple IV sites may not be available in critically ill neonates, which may necessitate coadministration or administration in adjacent lumens of a central line.

EBOV-infected neonates would likely need IV nutrition support, at a minimum, IV dextrose, so that they do not become hypoglycemic during the infusion. This population of neonates may also require additional medications for life support, including vasopressors. In the critically ill neonate, if multiple IV sites are not available, clinicians could use their discretion in the administration of multiple life-saving medications.

Conclusion

To address the issue regarding excess endotoxin and the unique administration challenges in neonates, the following modifications to Section 2.2 Preparation, Administration and Storage Instructions of the proposed label have been made:

(1) Amendments that provide acceptable endotoxin levels in total infusion volumes for pediatric patients with body weight ≤16 kg.

(2) Instructions to use a syringe pump for neonates weighing 0.5 to (b) (4)

(3) Instructions to avoid simultaneous coadministration of other drugs through the same infusion line. However, clinicians are expected to use their discretion if a life-saving drug(s) must be administered, particularly in a situation with a neonate or other patient with limited IV access.

7.7.2. Development of Resistance Against Ansuvimab-zykl Has Not Been Adequately Characterized

Issue

Limited resistance data were provided to identify resistance pathways for ansuvimab-zykl, and no clinical or relevant animal study fully characterized the potential for the emergence of clinically significant resistant substitutions associated with ansuvimab-zykl. Amino acid substitutions associated with reduced susceptibility of ansuvimab-zykl have not been identified to date.

Background

Cell Culture Selection Experiments

The Applicant has not selected EBOV or EBOV GP pseudotype virus resistant to ansuvimab-zykl in cell culture or characterized several independent isolates genotypically and phenotypically to identify amino acid substitutions in GP that lead to reduced susceptibility to ansuvimab-zykl.

Identification of GP Substitutions Within the Ansuvimab-zykl Epitope

A study was performed to identify potential resistance-associated substitutions that were detected in EBOV GP sequences derived from samples collected from patients who were associated with the EBOV outbreak in the North Kivu province of the Democratic Republic of Congo in 2018. Of the 569 virus genomic sequences analyzed, there were 50 positions in subsequent isolates that had amino acid changes (relative to the initial EBOV variant), representing 49 unique EBOV GP variants. One of these substitutions, GP_L111I, occurred at a position that is part of the ansuvimab-zykl epitope, which was defined as 111-119, LEIKKPDGS. Of note, 12 substitutions were detected in the EBOV sequences from two or more subjects, but none of these positions were within 10 Angstroms of the residues that comprise the ansuvimab-zykl epitope. Ansuvimab-zykl retained nearly equivalent neutralization activity against EBOV variants that were predominantly circulating in August 2018, June 2019, and December 2019. The EBOV GP_L111I substitution that occurred in the ansuvimab-zykl epitope was not assessed for its impact on susceptibility to the mAb.

Ansuvimab-zykl Resistance Data From Clinical Trials

No clinical studies evaluating resistance to ansuvimab-zykl have been conducted.

Assessment

The Clinical Virology reviewer reviewed the totality of the resistance data provided by the Applicant and concluded that the data provided were insufficient to adequately characterize resistance to ansuvimab-zykl. The review team was notified of the incomplete characterization of resistance, and it was agreed that additional resistance data would be requested as postmarketing requirements (PMRs) and PMCs (Section 22).

Conclusion

The incomplete characterization of resistance described in this section will be addressed by two PMRs related to further characterizing resistance to ansuvimab-zykl. A PMC has been agreed upon with the Applicant to assess ansuvimab-zykl resistance in samples collected in the PALM Trial if those data become available from the sponsor of that trial.

Additional details are provided in Section 22.

7.7.3. Potential Risks of Immunogenicity

Issue

Immune responses to therapeutic protein products have the potential to impact product pharmacokinetics, pharmacodynamics, safety, and efficacy. The key safety concerns associated with immunogenicity are: anaphylaxis, hypersensitivity, and other infusion-related reactions.

Background

An immunogenicity assessment was conducted in Study18-I-0069, following administration of a single dose of ansuvimab-zykl in healthy adult volunteers. Predose and postdose samples obtained on study Days 28 and 56 were evaluated for the presence of anti-ansuvimab-zykl antibodies. Because ansuvimab-zykl was administered as a single dose in all clinical studies, there were no opportunities to evaluate immunogenicity following repeat-dose administration. No immunogenicity assessments were conducted in EBOV-infected patients.

Assessment

Two predose serum samples were obtained from healthy subjects who tested positive for ansuvimab-zykl ADAs in the screening immunogenicity assay. However, the ADA positivity of these samples was not verified in a confirmatory assay as recommended by the FDA's guidance on Immunogenicity Testing of Therapeutic Protein Products. No ADAs against ansuvimab-zykl were detected in serum samples obtained from healthy subjects on Days 28 and 56. Per the OBP reviewer's assessment (please see the OBP Immunogenicity Review by Dr. Davinna Ligons uploaded to Panorama on 12/16/2020), the immunoassay developed for ADA detection was sub-optimally validated. Consequently, the reliability of the ADA data from Study 18-I-0069 is unknown.

Conclusion

The review team declined to pursue a PMC/PMR to revalidate the immunoassay and re-analyze Study 18-I-0069 serum samples for the presence of ADAs because this would provide limited additional information. While it would inform the reliability of the data generated in Study18-I-0069, it would not provide a definitive assessment of immunogenicity. Because immunogenicity testing was limited to healthy volunteers, the potential for ADA induction and its clinical consequences in EBOV-infected patients would remain unknown. Given that ansuvimab-zykl targets an exogenous viral protein and is intended for single dose administration, the overall potential for immunogenicity is expected to be low. Therefore, additional clinical studies evaluating immunogenicity are not warranted at this time. However, modifications to the language in Subsection 6.2 (Immunogenicity) of the labeling are warranted.

8. Therapeutic Individualization

8.1. Intrinsic Factors

The PK of ansuvimab-zykl was only characterized in healthy adults aged 22 to 56 with normal BMI and normal renal and hepatic function. Consequently, the effect of age (pediatric or geriatric), organ impairment (renal or hepatic), pregnancy, or EBOV infection on the PK of ansuvimab-zykl has not been evaluated. As a therapeutic protein (>40 kDa), ansuvimab-zykl is expected to be eliminated by degradation through protein catabolism. Therefore, the PK of ansuvimab-zykl is not expected to be substantially altered in patients with renal impairment. Limited information is available on the potential impact of hepatic impairment on the PK of mAbs. If feasible, we recommend evaluating the PK of ansuvimab-zykl in EBOV-infected patients during future outbreaks. This would allow assessment of exposure-response relationships (for both safety and efficacy) and the impact of baseline and demographic characteristics on PK.

8.2. Drug Interactions

Enzyme- or Transporter-Mediated Interactions

As a mAb targeting an exogenous viral protein, ansuvimab-zykl is not expected to be a victim or perpetrator of metabolizing enzyme- or transporter-mediated drug interactions. Therefore, neither in vitro nor in vivo DDI studies were conducted.

Vaccine Interactions

Vaccine-therapeutic interaction studies have not been conducted in humans using ansuvimab-zykl. The efficacy of ansuvimab-zykl in patients who received a live recombinant EBOV vaccine prior to enrollment in the PALM Trial and MEURI EAP was comparable to that of patients who did not receive the vaccine. However, there is a potential for ansuvimab-zykl to inhibit replication of live vaccine virus, thus possibly reducing the efficacy of the vaccine. For this reason, the labeling recommends avoiding concurrent administration of live vaccine during treatment with ansuvimab-zykl.

8.3. Plans for Pediatric Drug Development

Ansuvimab-zykl was granted Orphan Drug Designation (#2019-6830) for the treatment of patients with EBOV infection on May 8, 2019. With this designation, it was exempted from the Pediatric Research Equity Act requirements. Nevertheless, adequate clinical experience was provided to evaluate the benefit and potential risks in the pediatric population, including neonates born to EBOV-infected mothers. The review issue relevant to the evaluation of benefit for pediatric populations is discussed in Section 6.3.3. The review issue relevant to the evaluation of risk associated with the proposed total volumes for infusion and the proposed total infusion volumes and infusion times for neonates is discussed in Section 7.7.1.

8.4. Pregnancy and Lactation

As ansuvimab-zykl is directed against an exogenous target, no reproductive or development toxicology studies were performed in accordance with ICH S6(R1). There were no signs of reproductive or developmental toxicity in either the repeat-dose toxicology study in rhesus monkeys or in the tissue cross-reactivity study in adult human tissues. Ansuvimab-zykl is therefore not anticipated to affect pregnancy or lactation. A tissue cross-reactivity study in human fetal tissues is requested as a PMC.

The safety of Ebanga for the treatment of *Zaire ebolavirus* was evaluated in the PALM Trial, where a total of 173 patients (119 adults including 5 pregnant women and 54 pediatric patients) received ansuvimab-zykl 50 mg/kg IV as a single infusion, and 168 patients received an investigational control. Both arms received optimized standard of care treatment. Pregnancy outcomes are available for five pregnancies identified during the PALM RCT (Table 36). No data are available for pregnant women in the PALM-Extension Phase or the MEURI EAP. This data for Ebanga is insufficient to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Table 36. Pregnancy Outcomes Following Exposure to Ansuvimab-zykl During PALM Trial (n=5)

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

Subject ID	Maternal Age (Years)	Reported Drug Exposure	Timing of Exposure	Maternal Outcome	Fetal Outcome
(b) (6)	34 y.o. Gravida 6 Para 5	Ansuvimab-zykl	2nd trimester (22 weeks gestation)	**Maternal survival** at 58-day follow-up	**Fetal death in utero** (8 weeks after treatment the patient delivered a 1st degree macerated fetus with no visible malformations. The fetal death was reported as unrelated to ansuvimab-zykl).
(b) (6)	28 y.o. Gravida 4 Para 3	Ansuvimab-zykl	2nd trimester (24 weeks gestation)	Maternal survival at 58-day follow-up	**Fetal death in utero** (25 days after treatment the patient delivered a 2nd degree macerated fetus).

Source: Table created by reviewer based on text narrative in Applicant's Clinical Study Report Section 12.3.5.2, page 81 of 94.
Abbreviations: PALM, PAmoja TuLinde Maisha; RCT, randomized controlled trial, y.o., years old

The high rate of maternal and fetal morbidity and mortality observed in the PALM Trial are consistent with the published literature regarding the risks to pregnancy associated with underlying maternal *Zaire ebolavirus* infection. Because EBOV is life-threatening for both the mother and fetus, treatment should not be withheld due to pregnancy.

For Pregnancy and Lactation Labeling Rule (PLLR) labeling, the Risk Summary in Subsection 8.1 Pregnancy will reflect the above conclusions. The PLLR background risk statement will be omitted because it may be misleading considering that the rate of miscarriage in patients infected with EBOV is much higher than the reported 15 to 20% in the U.S. general population. The indication-specific background risk statement will also be omitted because it is inapplicable considering that infection with EBOV is life-threatening for both the mother and fetus, and treatment should not be withheld due to pregnancy. In addition, a Clinical Consideration will be included that maternal, fetal, and neonatal outcomes are poor among pregnant women infected with EBOV, 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. Subsection 8.3 of Ebanga labeling for Females and Males of Reproduction Potential will be omitted given that there are no available human or animal studies evaluating the effect of ansuvimab-zykl on male or female fertility. Similarly, pregnancy testing and contraception subheadings are not applicable because there are no available data to suggest ansuvimab-zykl use is associated with embryo-fetal toxicity. Finally, because monoclonal antibodies, such as Ebanga, are transported across the placenta, Ebanga has the potential to be transferred from the mother to the developing fetus.

PALM-Extension Phase

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

MEURI Expanded Access Protocol

The Applicant stated in their response to DPMH's IR that pregnancy data from the MEURI EAP are also currently unavailable. The Applicant noted this data were collected by the WHO and no pregnancy-related information has been shared despite requests for additional data. Finally, the

Applicant stated the WHO has not communicated an intent to share additional information nor a timeframe for any further update.

Lactation

There are no available data on the presence of ansuvimab-zykl in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to ansuvimab-zykl are unknown. Both the Centers of Disease Control and the WHO recommend that women with *Zaire ebolavirus* infection not breastfeed due to the reported presence of Ebola virus in breast milk and the potential for postnatal transmission in the breastfeed infant.

For PLLR labeling, the Risk Summary in Subsection 8.2 Lactation will reflect the above conclusions and include a statement that the Centers of Disease Control recommends that mothers infected with EBOV not breastfeed their infants to the reduce the risk of postnatal transmission of EBOV.

9. Product Quality

Approval with PMCs - The Office of Pharmaceutical Quality (OPQ), CDER recommends approval of STN 761172 for Ebanga manufactured by (b) (4) for Ridgeback Biotherapeutics, LP. The data and information submitted in this application are sufficient to support the conclusion that the manufacture of Ebanga is well controlled and leads to a product that is pure and potent for the duration of the product shelf life. OPQ recommends that this product be approved for human use under the conditions specified in the package insert. The chemistry, manufacturing, and controls postmarketing commitments between OPQ and the Applicant are listed below should be included in the action letter:

Table 37. Chemistry, Manufacturing, and Controls Postmarketing Commitments

PMC	Milestones
1. Qualify the bioburden test method for the (b) (4) with 3 batches of product using 10 mL samples	Final Report Submission: 12/2022
2. Submit a feasibility study protocol for an alternative endotoxin method to mitigate low endotoxin recovery (LER) in ansuvimab drug product. If a suitable endotoxin method is not identified by March 2021, continue to develop an alternative method and provide annual progress updates to the BLA. Once a suitable endotoxin method is identified, submit the LER final study report using three lots of ansuvimab.	Final Report Submission: 03/2021
3. Implement annual container closure integrity testing (CCIT) in lieu of sterility testing in the stability program for ansuvimab drug product and submit the CCIT method validation report. The CCIT method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (b) (4)	Final Report Submission: 12/2021
4. Provide data from three real-time shipments to demonstrate that shipping temperature of 2-8°C is maintained within the insulated shippers for finished drug product when exposed to summer and winter conditions.	Final Report Submission: 09/2022

PMC	Milestones
5. To develop and implement a fully validated virus neutralization potency assay with appropriately justified acceptance criteria for release and stability testing of ansuvimab drug substance and drug product. The method validation data and updated drug substance and drug product release and stability specifications will be reported per 21 CFR 601.12	Final Report Submission: 03/2022
6. To conduct comprehensive compatibility and in-use stability studies to support the storage, handling, preparation, dilution scheme, and administration conditions and materials described in the ansuvimab labeling and to support the stability of drug product quality attributes during administration. The compatibility studies and in-use stability studies will include evaluation of 5% dextrose as a diluent to support the administration of drug product to neonates. The labeling will be updated based on the results from these studies. The final compatibility study data and updates to the labeling will be reported per 21 CFR 601.12	Final Report Submission: 03/2022
7. To perform extractables/leachables studies and risk assessments to evaluate leachables from the container closure system(s) and manufacturing product conduct surfaces of ansuvimab drug substance and drug product and assess the potential impact of leachables on product quality at the end of drug product shelf-life. The analyses will be performed using drug substance and drug product lot(s) and/or representative samples (e.g. (b) (4), if justified) analyzed at appropriate time points, including at the end of drug product shelf life. Appropriate methods will be used to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals. Characterization of the potential impact on product quality will be assessed using adequate analytical methods. Complete data and the risk evaluation for the potential impact of leachables on product safety and quality will be provided in the final study report per 21 CFR 601.12.	Final Report Submission: 03/2022
8. To conduct studies to confirm clearance of process related impurities from the commercial scale drug substance manufacturing process and a risk assessment for the residual levels of impurities on patient safety. The results from these studies and risk assessment will be provided in the final report to the BLA per 21 CFR 601.12.	Final Report Submission: 03/2022
9. To conduct viral clearance studies using four model viruses relevant to the ansuvimab drug substance manufacturing process using a scaled down model representative of the commercial process. The analysis should consist of an assessment of virus titer before and after each step tested in two independent studies using an assay with adequate sensitivity and reproducibility. The final viral clearance report will be submitted to the BLA per 21 CFR 601.12.	Final Report Submission: 03/2022

PMC	Milestones
10. To assess the coverage of the HCP assay to confirm sensitivity. The assessment should be conducted using 2D SDS-PAGE gels of the range of HCPs detected by a sensitive protein stain, such as silver stain, compared to the range detected by western blot analysis using the antibodies employed in the assays or an assay that is demonstrated to be equally or more sensitive than western blot. The approximate percentage of HCP impurities that are recognized by the HCP antibodies will be provided from an appropriate number of ansuvimab drug substance lots. The validation data and updates to the drug substance control strategy, if applicable, will be provided in the final report to the BLA per 21 CFR 601.12.	Final Report Submission: 03/2022
11. To further characterize the potential contribution of antibody-dependent cellular cytotoxicity (ADCC) activity to the mechanism of action of ansuvimab and to assess all accessible clinical and PPQ lots for ADCC activity. If the data confirm that ADCC activity contributes to the mechanism of action or if ADCC activity cannot be ruled out as a potential MOA, update the control strategy to ensure that ADCC activity is adequately controlled. The final characterization study results and assay validation reports and updates to the drug substance and drug product control strategy, if applicable, will be submitted to the BLA per 21 CFR 601.12.	Final Report Submission: 03/2022
12. To develop and implement a control strategy for the (b) (4) excipient in ansuvimab drug substance and drug product. The control strategy may include a validated (b) (4) assay with appropriately justified acceptance criteria for release and/or stability testing of ansuvimab drug substance and drug product. The updated drug substance and drug product control strategy and supporting data will be reported per 21 CFR 601.12	Final Report Submission: 03/2022
13. To provide data confirming that the lower action limit for the critical process parameter and in-process control of drug product fill weight in section 3.2.P.3.4 supports the withdrawal of 8 mL per drug product vial following reconstitution and the concentration of drug product is within appropriate range. The final report and updates to the drug product control strategy and supporting data will be reported per 21 CFR 601.12.	Final Report Submission: 03/2022

9.1. Device or Combination Product Considerations

This section is not applicable, because ansuvimab-zykl does not involve components that would normally be regulated under different types of regulatory authorities.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

The Office of Scientific Investigations (OSI) conducted an inspection of the records from four Ebola Treatment Units, Beni, Katwa, Mangina, and Butembo, and the study sponsor, the

National Institute of Allergy and Infectious Disease (NIAID), in support of BLA 761172. The inspections covered one clinical trial, Protocol 19-I-0003, the PALM Study, which included nine clinical investigators who rotated through, staffed, and supervised the conduct of the study for the four ETUs.

Due to the FDA restrictions on conducting inspections in the DRC, inspections of the 4 ETUs were authorized to be conducted at NIAID in Bethesda, MD. NIAID provided inspectors access to the PALM Trial website (contained scanned copies of the paper case report forms), the Huddle Database (contained scanned copies of the informed consent documents and GeneXpert source records), and the REDCap electronic data capture system used during the conduct of the trial (contained the case report form data). Four clinical investigators were selected to represent the four ETUs during the inspections to answer questions.

Table 38. Study Sites Requested for Inspection

Name	Location	Notes
Jean-Luc Biampata, MD	Beni, DRC	337 subjects were screened, 335 were randomized [REGN-EB3 (n=72), ZMapp (n=84), ansuvimab-zykl (n=89), and remdesivir (n=90)] and 196 subjects completed the study.
Ali Dilu, MD	Katwa, DRC	46 subjects were screened, 46 subjects were screened, 46 were randomized [REGN-EB3 (n=10), ZMapp (n=12), ansuvimab-zykl (n=12), and remdesivir (n=12)], and 27 subjects completed the study.
Isekusu Mpinda Fiston, MD	Mangina, DRC	57 subjects were screened, 57 subjects were screened, 57 were randomized [REGN-EB3 (n=14), ZMapp (n=13), ansuvimab-zykl (n=15), and remdesivir (n=15)] and 14 subjects completed to the study.
Vicky Malengera, MD	Butembo, DRC	244 subjects were screened, 57 subjects were screened, 57 were randomized [REGN-EB3 (n=14), ZMapp (n=13), ansuvimab-zykl (n=15), and remdesivir (n=15)] and 70 subjects completed the study
National Institute of Allergy and Infectious Disease (NIAID)	Bethesda, MD USA	Responsible for control, oversight, and management of Protocol 19-I-0003. NIAID contracted with Leidos Biomedical Research, Inc. for clinical trial management, regulatory documentation, and data management. Documentation relied on the PALM Trial Website, the Huddle Database, and the REDCap electronic data capture system.

OSI concluded that the PALM Trial was conducted adequately, and the study data submitted, including the primary efficacy endpoint data, appear acceptable in support of the respective indication. Please refer to Section 20 for the Clinical Inspection Summary from OSI.

11. Advisory Committee Summary

This application was not taken to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected and there were no controversial issues that would benefit from discussion by an advisory committee.

III. Appendices

12. Summary of Regulatory History

IND 138090 was submitted on January 25, 2018 by the National Institute of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center (VRC), to study VRC-EBOMAB092-00-AB (mAb114) referred to as ansuvimab-zykl, for the indication of treatment of *Zaire ebolavirus* (EBOV) infection. Ansuvimab-zykl is a recombinant, fully human IgG1 monoclonal antibody (mAb) that blocks binding of the glycan cap and glycoprotein (GP) domain of the Zaire ebolavirus to the cell receptor, preventing virus entry into the cell, and was determined safe to proceed for a first-in-human Phase 1 study in Febuary followed by the Agency's official study may proceed letter on March 5, 2018.

The announcement of the 9th Ebola outbreak on May 8, 2018 in the Bikoro Health District, Democratic Republic of the Congo (DRC) and 10th Ebola outbreak in the North Kivu Region, DRC on August 1, 2018, resulted in Agency guidance on the use of ansuvimab-zykl. As a result of this guidance, ansuvimab-zykl was used as an investigational therapeutic in an open-label, intermediate expanded access protocol (EAP) for Ebola virus infected patients or high-risk EBOV postexposure prophylaxis.

With the announcement of the 10th Ebola outbreak, NIAID and the DRC's Institut National de la Recherche Biomédicale (INRB) began a randomized trial on November 20, 2018 in the DRC. Conducted under NIH-19-I-0003 protocol and referred to as the PAmoja TuLinde Maisha randomized, controlled trial (PALM RCT), this study was a Phase 2/3 open-label randomized, controlled trial, in children and adults (including pregnant women) with laboratory-confirmed EBOV infection designed to study the comparative safety and efficacy of four investigational therapeutics for the treatment of EBOV.

On December 13, 2018, it was announced that the NIH issued a nonexclusive license of ansuvimab-zykl intellectual property to Ridgeback Biotherapeutics, LP for continued development as a therapeutic for Ebolavirus disease. On January 28, 2019, Ridgeback Biotherapeutics, LP submitted a pre-IND Type B meeting request under pre-IND 142584 to obtain feedback and guidance from the Agency on ansuvimab-zykl on: 1) a future IND submission, 2) proposed nonclinical and clinical studies to support licensure of ansuvimab-zykl as a treatment for EBOV infection via the Animal Rule pathway (*21 CFR Part 601.90 through 601.95*), and 3) utilization of human efficacy data from the ongoing PALM RCT to limit the number of animal studies required for approval.

In response to this meeting request on January 28, 2019, the Agency provided feedback via Type B, Written Responses Only on March 27, 2019 with guidance to support the continued development of ansuvimab-zykl.

Notable Regulatory Milestones for This Application Include:

- On May 8, 2019, Orphan Drug Designation request was granted for ansuvimab-zykl via Ridgeback-sponsored pre-IND 142584 for the indication of treatment of EBOV infection, thus exempting the Sponsor from any Pediatric Research Equity Act requirements

- On August 12, 2019, the independent data and safety monitoring board (DSMB) recommended early termination of PALM RCT due to favorable results with two of four candidates and all future patients randomized to receive either REGN-EB3 or ansuvimab-zykl for an extension phase of the trial
- On August 19, 2019, the NIAID VRC transferred sponsorship of IND 138090 to Ridgeback Biotherapeutics, LP
- On August 26, 2019, Ridgeback Biotherapeutics, LP submitted a Breakthrough Therapy Designation Request for ansuvimab-zykl for the indication of treatment of EBOV infection which was granted by the Agency on September 6, 2019
- On September 24, 2019, the Agency provided guidance to Ridgeback Biotherapeutics, LP that would support a traditional approval instead of the Animal Rule pathway in light of preliminary findings from the PALM RCT, which established the primary efficacy of ansuvimab-zykl
- On December 12, 2019, Ridgeback Biotherapeutics, LP submitted a request for rolling submission and review of a planned BLA for the treatment of EBOV infection, which was granted by the Agency on December 19, 2019
- On May 29, 2019, the final piece of BLA 761172 as a rolling submission was submitted and acknowledged by the Agency on June 16, 2020
- Ridgeback's proposed proprietary name, Ebanga, was found acceptable by the Agency on July 23, 2020 and the nonproprietary name, ansuvimab-zykl, was found conditionally acceptable on September 3, 2020.

Notable Regulatory Milestone Meetings for This Application Include:

- A Type B, pre-BLA chemistry, manufacturing, and controls meeting was requested on November 8, 2019, granted on November 22, 2019, and preliminary comments were issued on January 6, 2020. Ridgeback Biotherapeutics, LP received the Agency's comments and a face-to-face meeting was held on January 8, 2020 to provide guidance on the required data elements and content requirements for the chemistry, manufacturing, and controls portion of the BLA.
- A Type B, pre-BLA clinical/pharmacology/toxicology meeting, which also served as the Breakthrough Therapy Initial Comprehensive Meeting, was requested on November 7, 2019, granted on November 15, 2019, and preliminary comments were issued on December 18, 2019. Ridgeback Biotherapeutics, LP received the Agency's comments and a face-to-face meeting was held on January 10, 2020 to discuss the proposed content and format of the BLA.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

The nonclinical safety studies conducted to support ansuvimab-zykl were originally submitted to and reviewed under IND 138090. All pertinent studies were also submitted to the present BLA and are reviewed in the following sections.

13.1.1. Pharmacology (Primary and Secondary)

Ansuvimab-zykl is a human IgG1 monoclonal antibody against the glycan cap and GP1 domain of EBOV glycoprotein derived from a survivor of the 1995 Ebola virus outbreak in Kikwit and is intended for the treatment of *Zaire ebolavirus* infection. The activity of ansuvimab-zykl was evaluated in three in vivo proof-of-concept studies in which rhesus monkeys were challenged with uniformly lethal doses of Kikwit 8U EBOV (1000 pfu). These studies demonstrated that a single dose of 50 mg/kg ansuvimab-zykl prevented EBOV-induced mortality in these animals as late as 5-days postchallenge relative to controls. Doses as low as 30 mg/kg ansuvimab-zykl administered 1-day postchallenge also protected against EBOV-induced mortality. In total, all ansuvimab-zykl-treated animals survived EBOV challenge while all control animals succumbed within 10 days. Please refer to the virology review in Section 18 for more information.

13.1.2. Safety Pharmacology

Assessments of safety pharmacology (electrocardiography, blood pressure, respiratory rate, and a neurological evaluation) were performed in the 4-week repeat-dose toxicology study in rhesus monkeys (Study #1016-1363). No drug-related changes in cardiac or neurological parameters were observed. Respiratory rate was decreased 27% in mid-dose males 1-hour postdose on Day 8, but this was considered unrelated to treatment as it was attributed to a single animal and was not dose-related. Please refer to the 4-week toxicology study review in Section 13.1.4 for more information.

13.1.3. Pharmacokinetics

The pharmacokinetics (PK)/toxicokinetics of ansuvimab-zykl were evaluated in the 4-week repeat-dose toxicology study in rhesus monkeys (Study #1016-1363). Toxicokinetic parameters from this study are presented in the following table (Table 39). Biodistribution of ansuvimab-zykl was also evaluated in this study by immunofluorescence. Tissues from the brain, lung, liver, kidneys, spleen, and mesenteric lymph node were selected from one animal/sex from the control, low-dose, and mid-dose groups at Day 25, and from one animal/sex from the low-dose and mid-dose groups only at Day 79. At Day 25, ansuvimab-zykl was detected in endothelial blood vessels in the brain (endothelial blood vessels), lung (endothelial blood vessels; mid-dose only), liver (sinusoidal endothelium, Kupffer cells, and hepatocytes), kidneys (endothelial blood vessels and interstitial capillaries), spleen (follicular dendritic cells in germinal centers and macrophages in red pulp), and mesenteric lymph node (follicular dendritic cells in germinal centers). At Day 79, ansuvimab-zykl was detected only in the spleen (follicular dendritic cells in germinal centers

and macrophages in red pulp) and mesenteric lymph node (follicular dendritic cells in germinal centers). Ansuvimab-zykl was not detected in tissues from the control animals. In addition, GP binding activity was detected ex vivo in cerebrospinal fluid (CSF) samples from this study by enzyme-linked immunosorbent assay (ELISA), indicating that ansuvimab-zykl also distributed to the CSF. As the CSF measurements were qualitative, however, it is unclear how the retained pharmacological activity of ansuvimab-zykl in CSF correlates to the available in vitro activity data. Please refer to the 4-week toxicology study review in Section 13.1.4 or more information.

In addition, blood samples were collected from the 4-week toxicology study on Days 1, 8, 22, 29, 57, and 78 to measure immunogenicity, but these samples were not analyzed. No clear changes in drug exposure or ex vivo EBOV GP binding activity were observed in this study, suggesting that no meaningful anti-drug antibody formation occurred in this study.

Table 39. Toxicokinetic Data

Study Title (Study No.)	Major Findings
4-Week Intravenous Toxicity Study with an 8-Week Recovery Period in Rhesus Monkeys (Study #1016-1363) Sample collection times Groups 1, 2 and 4: • Days 1 & 22 pre-dose and 0.25, 2, 8, 24 and 72 hrs postdose Group 3: • Days 1, 2, 3, 22, 23 & 24 pre-dose and 0.25 hrs postdose All Groups: • Days 8 & 15 pre-dose • Days 29, 36, 43, 50, 57, 64, 71 & 78 NOAEL =500 mg/kg/dose (AUC_{last} =222664 µg.day/mL at Day 22, gender-averaged) Exposure multiple =7.6 Based on mean steady-state exposures in healthy adult human subjects receiving a single 50 mg/kg IV infusion ($AUC_{0\text{-}last}$ =29288 µg.day/mL)	TK data from Groups 2 and 4 only (Day 1, main and recovery groups): **DAY 1** **Group 2: 50 mg/kg/dose (1x/week)** **Group 4: 500 mg/kg/dose (1x/week)** **Sex** / **Male** / **Female** / **Male** / **Female** T_{max} (Day): 0.011 (0.001) / 0.025 (0.033) / 0.011 (0.000) / 0.011 (0.000) C_{max} (µg/mL): 1098 (147) / 1058 (119) / 12386 (1428) / 11619 (1608) C0 (µg/mL): 1122 (147) / 1069 (109) / 12613 (1469) / 11919 (1680) T_{last} (Day): 7.000(0.000) / 7.000 (0.000) / 7.000 (0.000) / 7.000 (0.000) C_{last} (µg/mL): 343 (63) / 386 (41) / 3653 (355) / 3390 (440) $AUC_{(last)}$ (Day*µg/mL): 3393 (526) / 3490 (375) / 36947 (3675) / 34060 (3923) TK data from Groups 2 and 4 only (Day 22, main group only): **DAY 22 MAIN** **Group 2: 50 mg/kg/dose (1x/week)** **Group 4: 500 mg/kg/dose (1x/week)** **Sex** / **Male** / **Female** / **Male** / **Female** T_{max} (Day): 0.035 (0.043) / 0.340 (0.571) / 0.059 (0.042) / 0.010 (0.000) C_{max} (µg/mL): 2593 (284) / 2348 (106) / 24714 (5656) / 18344 (4024) C0 (µg/mL): 2526 (302) / 2266 (209) / 24378 (7613) / 18511 (4136) T_{last} (Day): 3.000 (0.000) / 3.000 (0.000) / 3.000 (0.000) / 3.001 (0.001) C_{last} (µg/mL): 1354 (193) / 1417 (177) / 11586 (736) / 8781 (2564) $AUC_{(last)}$ (Day*µg/mL): 5103 (650) / 5394 (435) / 45798 (4045) / 34529 (8162) TK data from Groups 2 and 4 only (Day 22, recovery group only): **DAY 22 RECOVERY** **Group 2: 50 mg/kg/dose (1x/week)** **Group 4: 500 mg/kg/dose (1x/week)** **Sex** / **Combined Sexes** / **Combined Sexes** t½ (Day): 8.871 (5.596) / 14.555 (1.959) T_{max} (Day): 0.010 (0.000) / 0.029 (0.036) C_{max} (µg/mL): 2242 (276) / 24206 (3670) C0 (µg/mL): 2298 (274) / 24628 (4112) T_{last} (Day): 49.000 (14.000) / 56.000 (0.000) C_{last} (µg/mL): 49.71 (53.83) / 676 (140) $AUC_{(last)}$ (Day*µg/mL): 21014 (9248) / 222664 (16553) $AUC_{(0\text{-}\infty)}$ (Day*µg/mL): 21950 (10289) / 237090 (18228) V_z (mL/kg): 27.98 (13.06) / 44.38 (5.32) Vss (mL/kg): 30.20 (7.69) / 39.29 (4.82) CLss (mL/Day/kg): 2.73 (1.28) / 2.12 (0.16)

Study Title (Study No.)	Major Findings

TK data from Group 3 only (Day 24, recovery group only):

DAY 24 RECOVERY		Group 3 50 mg/kg/dose (3x/week)		Group 3 50 mg/kg/dose (3x/week)
	Sex	Male	Female	Combined Sexes
$t_{½}$	(Day)	7.611 (NC)	6.497 (NC)	7.054 (3.728)
T_{max}	(Day)	0.010 (NC)	0.010 (NC)	0.010 (0.000)
C_{max}	(µg/mL)	3816 (NC)	4347 (NC)	4081 (1605)
C0	ug/mL	3823 (NC)	4354 (NC)	4088 (1605)
T_{last}	(Day)	43.500 (NC)	54.000 (NC)	48.750 (10.500)
C_{last}	(µg/mL)	84 (NC)	11 (NC)	47.44 (79.82)
$AUC_{(last)}$	(Day*µg/mL)	39769 (NC)	35125 (NC)	37447 (26887)
$AUC_{(All)}$	Day*µg/mL	39769 (NC)	35125 (NC)	37447 (26887)
$AUC_{(0-\infty)}$	(Day*µg/mL)	41226 (NC)	35232 (NC)	38229 (28134)
V_z	(mL/kg)	21.86 (NC)	14.82 (NC)	18.34 (7.24)
Vss	(mL/kg)	13.55 (NC)	13.00 (NC)	13.27 (2.25)
CLss	(mL/Day/kg)	3.62 (NC)	1.59 (NC)	2.61 (2.55)

All values are presented as mean (standard deviation)

Source: From Applicant, study report RB-NCR-006-A1 (Text Tables 2-5), and Reviewer's analysis.

13.1.4. Toxicology

13.1.4.1. General Toxicology

A 4-Week Intravenous Toxicity Study With an 8-Week Recovery Period in Rhesus Monkeys (Study #1016-1363):

Key Study Findings

- NOAEL =500 mg/kg/dose (AUC_{last} =222664 µg.day/mL; maximum plasma concentration, C_{max} =24206 µg/mL on Day 22). No adverse, drug-related toxicities were observed up to the highest dose tested.
- Pathology findings in the heart (minimal to mild hemorrhage, dark red areas on the epicardium) were observed in one animal at Day 25 and three animals at Day 79. However, additional information provided by the Applicant on February 16, 2018, indicated that this was the result of perimortem changes associated with the euthanasia procedure and was unrelated to treatment.
- One mid-dose male exhibited weight loss and adverse clinical signs (decreased activity and appetite, limited usage and swelling of hind paws and limbs, profuse diarrhea) starting at Day 36 (12 days after conclusion of dosing) and was euthanized on Day 66. Cause of death was likely the result of a bacterial infection. As this occurred in a single animal at the mid-dose well after cessation of dosing, this was considered unrelated to treatment.

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 40. 4-Week Monkey Intravenous Toxicity Study Methods

Study Features and Methods	Details
Dose and frequency of dosing:	0, 50 (1x), 50 (3x) & 500 (1x) mg/kg/week
Route of administration:	IV infusion/bolus
Formulation/vehicle:	20mM histidine, 240mM sucrose, 0.02% (w/v) polysorbate 80, pH =6.0
Species/strain:	Rhesus monkeys
Number/sex/group:	3/sex/main group (euthanized on Day 25) 2/sex/recovery group (euthanized on Day 79)
Age:	22-46 months
Satellite groups/unique design:	No satellite groups. Mid-dose groups received 50 mg/kg ansuvimab-zykl 3x/week (Days 1, 2, 3, 8, 9, 10, 15, 16, 17, 22, 23 and 24). All other groups were dosed once weekly (Days 1, 8, 15 and 22). Drug was administered by IV bolus to low-dose and mid-dose animals, and by IV infusion to control and high-dose animals. Tissue distribution and EBOV GP binding activity of ansuvimab-zykl were evaluated in this study.
Deviation from study protocol affecting interpretation of results:	None

Table 41. 4-Week Monkey Intravenous Toxicity Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths during the dosing period. One mid-dose male was euthanized on Day 66, 6 weeks after the end of dosing, due to weight loss and adverse clinical signs (decreased activity and appetite, limited usage and swelling of hind paws and limbs, profuse diarrhea) starting at Day 36 (12 days after completion of dosing). Pathology findings included marked ulceration and severe suppurative inflammation in the colon, and mild erosion and moderate inflammation in the cecum. Gram-positive and Gram-negative bacilli were detected in phagocytic cells in the ulcerated areas, but it is unclear what species of bacteria were present or if they were pathogenic. Mild acute subdural hemorrhage in the spinal cord and marked acute hemorrhage in the skeletal muscle of the thigh, likely due to physical trauma, were also observed in this animal. Cause of death was inconclusive but was suspected to be bacterial in nature. As there was no correlation with dose level, timing, or exposure, this was considered unrelated to treatment.
Clinical signs	Examined once daily. No drug-related findings.
Local tolerance	Injection site reactions were evaluated with a modified Draize scoring scheme. Slight increases in erythema and edema were observed in all treated animals relative to controls throughout dosing, particularly at the mid-dose as these animals received three doses per week instead of one. These changes were not considered adverse due to their minor severity.
Body weights	Measured once weekly. No drug-related findings.
Food consumption	Measured qualitatively only. No drug-related findings.
Ophthalmoscopy	Evaluated pretreatment and once between Days 22 and 25. No drug-related findings.
Electrocardiography, blood pressure & respiratory rate	ECGs, blood pressures, and respiratory rates were recorded pretreatment, on Days 8 and 22, and during the last week of recovery. Respiratory rate was decreased 27% in mid-dose males 1-hour postdose on Day 8. This was considered incidental as it was attributed to a single animal and was not dose-related.

Parameters	Major Findings
Neurological examination	General observations, attitudinal and postural reactions, spinal segmental reflexes and tests of cranial nerve function were performed pretreatment, on Days 1 and 22, and during the last week of recovery. No drug-related findings.
Hematology/coagulation	Blood samples collected pretreatment and on Days 8, 25 and 79. No drug-related findings.
Clinical chemistry	Blood samples collected pretreatment and on Days 8, 25 and 79. No drug-related findings.
Urinalysis	Measured pre-treatment and on Days 8, 25 and 79. No drug-related findings.
Gross pathology	Evaluated at necropsy on Days 25 and 79. Dark red areas on the epicardium on both ventricles in the heart were observed in one high-dose female on Day 25. No findings were observed on Day 79. The heart finding corresponds to mild cardiac hemorrhage in the same animal at Day 25 (see Histopathology). Additional information provided by the Applicant on February 16, 2018 indicated that this was the result of perimortem changes associated with the euthanasia procedure and was not drug-related.
Organ weights	Evaluated at necropsy on Days 25 and 79. Spleen weight was increased 43% in high-dose females at Day 25, which corresponds to the histopathology findings in this organ. This was considered nonadverse due to the low severity.
Histopathology Adequate battery: Yes Peer review: Yes	Evaluated at necropsy on Days 25 and 79. The following were observed at Day 25: • Mild hemorrhage in the heart in one high-dose female. Minimal inflammation, coronary fat, and lymphocytic infiltration in heart in a second high-dose female. Minimal lymphocytic infiltration in heart also in one low-dose female and one mid-dose male. • Minimal increased germinal centers and increased lymphocytes at germinal centers in spleen in two low-dose and one high-dose males. Mild increased periarteriolar lymphocyte sheaths in one mid-dose male. The following were observed on Day 79: • Minimal hemorrhage in the heart in one high-dose male. Mild hemorrhage of the epicardium in one high-dose female, and mild hemorrhage of the epicardium and myocardium in one low-dose male. Minimal lymphocytic infiltration in heart in one mid-dose male (also one control male). Minimal inflammation of the epicardium in one control female. The mild hemorrhage in the heart at Day 25 corresponds to the gross pathology findings in the heart in the same animal (dark red areas in the epicardium). Additional information provided by the Applicant on February 16, 2018, indicated that this was the result of perimortem changes associated with the euthanasia procedure. No correlation of cardiac hemorrhage with minimal lymphocytic infiltration or inflammation, present in three animals at Day 25 and 3 animals at Day 79, was observed. Minimal to mild hemorrhage was also observed in multiple organs at all dose levels, including controls, with no clear dose-dependence. Further, no cardiac findings were observed in the animal that was euthanized prematurely on Day 66. The cardiac findings were therefore considered incidental and unrelated to treatment.

Parameters	Major Findings
Ex vivo EBOV GP binding activity	Measured by ELISA in serum and cerebral spinal fluid (CSF). Blood samples were collected on Days 1, 8, 15, 22, 25, 30, 37, 46 and 79 (also Days 3, 10, 17 and 24 at the mid-dose). CSF samples were collected at necropsy on Days 25 and 79. GP binding activity was not detected in control samples or samples from treated animals predose on Day 1. In serum, GP binding activity was increased dose-dependently 2 hours postdose at all dose levels and was decreased roughly 50% at all subsequent pre-dose time points, throughout the dosing period, and decreased gradually by about 95% throughout Day 79. In CSF, roughly dose-dependent increases in GP binding activity were detected at Day 25 and were not detectable at the low- and mid doses on Day 79. GP binding activity in the CSF was decreased 65%, but was still detectable, at the high dose on Day 79. These data indicate that the EBOV GP binding affinity of ansuvimab-zykl is retained in serum and CSF in vivo.

13.1.4.2. Genetic Toxicology

Genotoxicity studies have not been conducted with ansuvimab-zykl. In accordance with International Council for Harmonisation (ICH) S6(R1), genotoxicity studies are not required for biologics.

13.1.4.3. Carcinogenicity

Carcinogenicity studies have not been conducted with ansuvimab-zykl. In accordance with ICH S1A and ICH S6(R1), carcinogenicity studies are not required as ansuvimab-zykl will be administered as a single intravenous (IV) infusion.

13.1.4.4. Reproductive Toxicology

Dedicated reproductive toxicology studies have not been conducted with ansuvimab-zykl. In accordance with ICH S6(R1), reproductive toxicology studies are generally not required for biologics to exogenous targets. In addition, no male or female reproductive toxicities were observed in the 4-week repeat-dose toxicology study in rhesus monkeys (Study #1016-1363), and no off-target binding was observed in the tissue cross-reactivity study in human tissues (Study #20101338). A tissue cross-reactivity study in human fetal and/or neonatal tissues will be requested in a postmarketing commitment (PMC).

13.1.4.5. Other Toxicology/Specialized Studies

A Tissue Cross-Reactivity Study of EBV114 in Normal Human Tissues (Study #RB-NCR-007/20101338)

The potential cross-reactivity of ansuvimab-zykl was evaluated in 36 frozen normal adult human tissues (3 donors/tissue) at concentrations up to 10 µg/mL. Positive (cryosections of Expi 293ΔMuc Day 2 cells) and negative controls (cryosections of Expi 293Sham Day 2 cells, human anti-HIV IgG1 antibody, and PBS) produced appropriate responses. No off-target binding was observed with ansuvimab-zykl in any tissue under the conditions of this study.

Assessment of Polyspecificity and Binding to the Phospholipid Cardiolipin for Ansuvimab-zykl (Study #RB-NCR-003)

The polyspecificity of ansuvimab-zykl was evaluated by assessing its reactivity with Hep-2 cells by immunocytochemistry and binding to cardiolipin by ELISA (Study #RB-NCR-003). VRC01-LS, an anti-HIV-1 gp120 mAb was used as a negative control, and 4E10, an anti-HIV-1 gp41 mAb, was used as a positive control. Ansuvimab-zykl exhibited no reactivity with Hep-2 cells and no binding to cardiolipin, similar to VRC01-LS and well below that of 4E10, suggesting that ansuvimab-zykl has no polyspecific reactivity.

13.1.5. Excipients/Impurities/Degradants

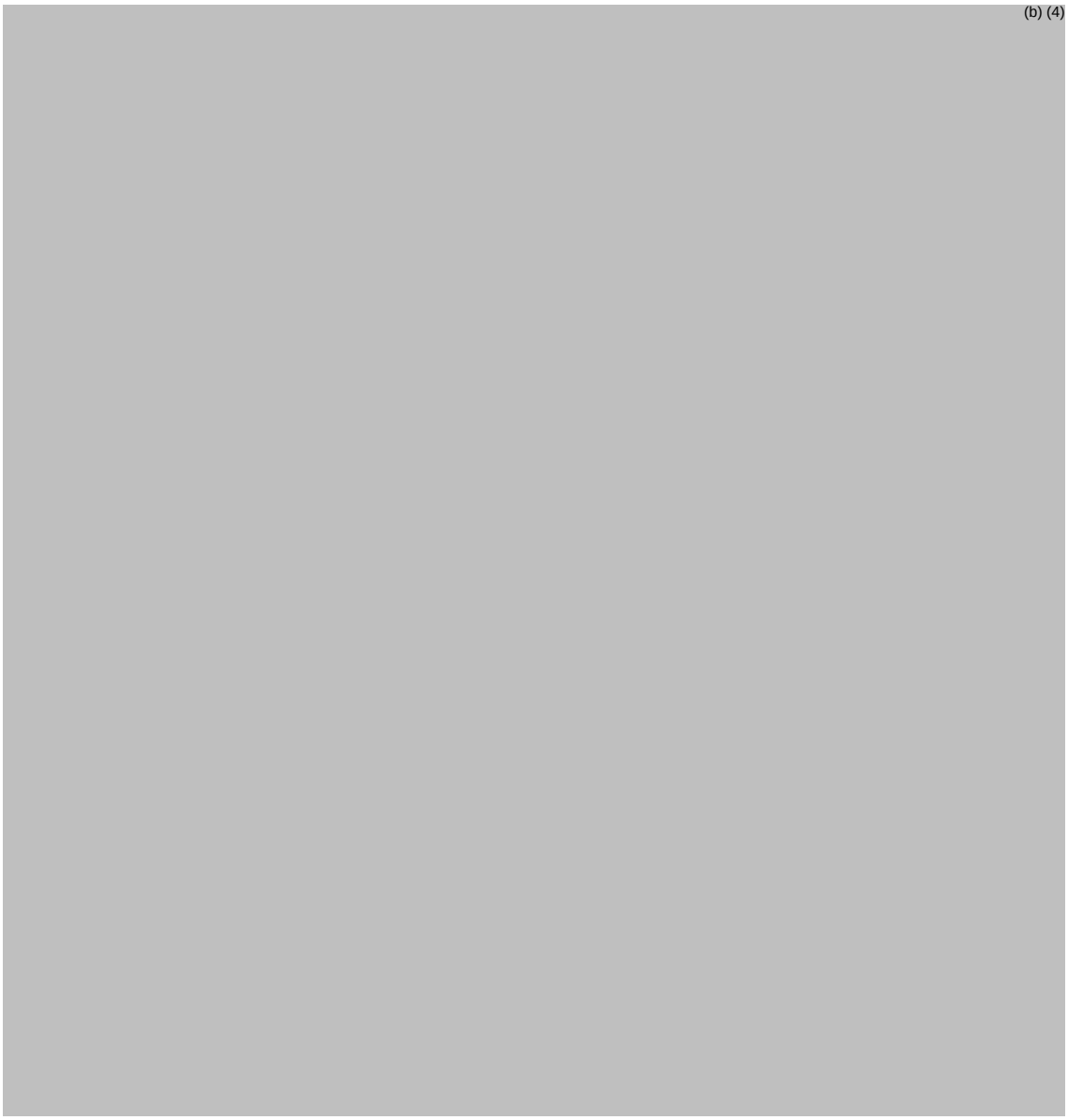
No excipient-related issues with the ansuvimab-zykl drug product have been identified. The qualification of actual and potential impurities that may arise during manufacture and storage of ansuvimab-zykl drug substance and product are described below. All impurities are categorized into process and product impurities and may arise from raw materials, manufacturing, and/or degradation. Overall, the proposed specifications, or lack of specifications, are considered acceptable from a pharmacology/toxicology perspective. This conclusion is based on the use of similar drug product lots in the pivotal nonclinical and clinical studies, forced degradation studies, a rabbit pyrogen test, and the fact that this product is administered as a single dose for a life-threatening indication. The drug product lots used in the pivotal nonclinical and clinical studies were also considered comparable from a product quality perspective.

Product-related impurities include high and low molecular weight species (aggregates and fragments), charged species, and post-translational modifications. Process-derived impurities include (b) (4) . The specifications for control of the ansuvimab-zykl drug substance are presented in Table 42. All acceptance criteria were met.

Three additional components, (b) (4), were identified as potential process-related impurities. (b) (4) have not been conducted but will be requested as postmarketing commitments. As the Applicant has indicated, the manufacturing process is presumed to remove any residual impurities to insignificant and safe levels. Considering that ansuvimab-zykl is administered as a single dose for a life-threatening indication, this reviewer considers the potential risk associated with (b) (4) to be low.

Table 42. Specifications for the Control of Ansuvimab-zykl Drug Substance

(b) (4)



Source: From Applicant, drug substance specifications (Table 1).

13.1.6. Extractables/Leachables

An assessment of extractables and leachables will be requested as a postmarketing commitment. No concerns have been identified based on an initial risk assessment.

13.2. Individual Reviews of Studies Submitted to the NDA

Not applicable.

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

Not applicable.

14.2. In Vivo Studies

Study 18-I-0069

Study 18-I-0069 is an open-label, single ascending dose study to evaluate the safety, tolerability, and PK of ansuvimab-zykl in healthy adults.

Methods

Healthy adults aged 22 to 56 years old were enrolled into three cohorts to receive ansuvimab-zykl doses of either 5 mg/kg (n=3), 25 mg/kg (n=5), or 50 mg/kg (n=10) administered as an IV infusion over 30 min. Serum samples for quantitation of ansuvimab-zykl concentrations were obtained predose and postinfusion through Day 168. Serum samples were also obtained for assessment of immunogenicity at baseline, at Day 28, and Day 168. PK and immunogenicity assessments were completed in subjects with at least 28 days or 56 days of data. Ansuvimab-zykl serum concentrations were measured using an insufficiently validated ELISA method (Section 14.2.2).

Results

Nineteen healthy adult subjects were enrolled in the study; however, one subject was terminated due to poor venous access. Subjects were predominantly female (61%) and white (72%). Concomitant medications were used in 10 patients and included: over-the-counter supplements (magnesium, vitamin D, iron, magnesium, l-methyl folate, and multivitamins), antidepressants (paroxetine, bupropion, and fluoxetine), an anxiolytic (buspirone), an anti-convulsant (topiramate), and intrauterine birth control devices (Paragard and Mirena). The use of these concomitant medications is not expected to influence the exposure of ansuvimab-zykl. Protocol deviations in this study were minor and were primarily due to delayed study visits and incomplete bloods draws.

The observed mean C_{max} was approximately dose-proportional between 5 mg/kg and 50 mg/kg, while $AUC_{0\text{-}inf}$ increased more than dose-proportionally between the same dose range. However, interpretation of this data is limited by the small number of subjects in each dose cohort. Both the long mean half-life, which ranged from 20 to 32 days, and the small estimated volume of distribution (V_{dz}), ranging from 57.7 to 69.6 mL/kg, associated with ansuvimab-zykl are characteristic of other IgG1 mAbs (Table 43).

Table 43. Mean (SD) of PK Parameters in Healthy Adult Subjects Administered a Single IV Dose of Ansuvimab-zykl

PK Parameter	5 mg/kg	25 mg/kg	50 mg/kg
C_{max} (µg/mL)	198.5 (45.1)	829.4 (237.4)	1932.3 (301.5)
$AUC_{0\text{-}inf}$ (day·µg/mL)	2372.6 (815.5)	16793.9 (996.2)	30864.7 (5501.7)
$t_{1/2}$ (day)	20.0 (10.5)	32.3 (1.5)	31.6 (4.9)
CL (mL/day/kg)	2.24 (0.77)	1.49 (0.09)	1.66 (0.26)
V_{dz} (mL/kg)	57.7 (12.0)	69.6 (5.7)	74.5 (10.4)

Source: from clinical pharmacology reviewer, assembled from Table 10 in study report 18-1-0069.
Abbreviations: $AUC_{0\text{-}inf}$, AUC from zero extrapolated to infinity; CL, total body clearance; C_{max}, maximum plasma concentration; $t_{1/2}$, elimination half-life; V_{dz}, terminal phase volume of distribution

14.2.1. Comparison of PK in NHP and Humans

Studies

Study 18-I-0069 was the only study to evaluate PK in humans; no PK assessments were performed in EBOV-infected patients.

No independent pharmacokinetic studies were conducted in NHP. Instead, the PK of ansuvimab-zykl in uninfected male and female NHP was obtained from a 4-week, GLP-compliant, repeat-dose toxicokinetic study (RB-NCR-19-006, RB-NCR-19-006-A1). Ansuvimab-zykl was administered either by slow bolus injection or 15-min infusion at doses of 50 mg/kg weekly (n=6), 50 mg/kg three times weekly (n=6), or 500 mg/kg weekly (n=6). Blood sampling was conducted through Day 25 for assessment of ansuvimab-zykl exposure. No PK assessments were performed in infected NHP.

Comparison of Ansuvimab-zykl Exposures

Single doses of 30 mg/kg or 50 mg/kg of ansuvimab-zykl were determined to be fully protective against a lethal dose of EBOV in proof-of-concept efficacy studies (RB-NCR-19-001, RB-NCR-19-002) conducted in NHP. Given the paucity of exposure data, exposures were only compared for the highest dose evaluated in Study 18-I-0069 in uninfected human subjects and the 50 mg/kg weekly dose in uninfected NHP. Ansuvimab-zykl $AUC_{0\text{-}inf}$ was 1.4-fold higher in uninfected humans following a single dose of 50 mg/kg compared to $AUC_{0\text{-}inf}$ resulting from the administration of 50 mg/kg weekly for 4 weeks in NHP (Table 44). The results of the proof-of-concept studies in NHP taken together with the moderately higher exposure associated with the 50 mg/kg in healthy humans provided justification for use of 50 mg/kg in the PALM Trial and MEURI EAP. However, the outcomes of the PALM Trial and MEURI EAP suggest that 50 mg/kg may not be the optimal dose for EBOV-infected patients with high baseline viral loads. Because only one dose level was evaluated and no dose-ranging clinical trials for efficacy were conducted, there is insufficient information to inform dose optimization. (Section 6.3.3).

Table 44. Comparison of Mean (SD) Exposures in Uninfected Humans and NHP

Species	C_{max} (µg/mL)	$AUC_{0\text{-}inf}$ (day·µg/mL)
Human	1932.3 (301.5)	30864.7 (5501.7)
NHP	2242 (276)	21950 (10289)

Source: from clinical pharmacology reviewer, assembled from clinical study report 18-1-0069 (Table 10) and preclinical study 1016-1363 report 1 (Table 8).
Abbreviations: $AUC_{0\text{-}inf}$, AUC from zero extrapolated to infinity; C_{max}, maximum plasma concentration

14.2.2. Bioanalytical

Measurement of Ansuvimab-zykl in Serum of Uninfected Humans (Validation Report)

Ansuvimab-zykl concentrations in serum samples were measured using an inadequately validated sandwich ELISA assay. Therefore, the reliability of ansuvimab-zykl serum concentration data reported for Study 18-I-0069 is unknown (Section II.6.3.5).

Measurement of Ansuvimab-zykl in Serum of Infected Humans

Not applicable. Ansuvimab-zykl concentrations were not determined from the blood samples collected in the PALM Trial and MEURI EAP.

Measurement of Ansuvimab-zykl in Serum of Uninfected NHP (Validation Report, Sample Analysis Report 1, Sample Analysis Report 2)

During validation and analysis of Study RB-NCR-19-006 toxicokinetic samples, accuracy and precision values for calibration, and QC samples were ≤20% (and ≤25% at the upper and lower limits of quantification). Samples were assayed within the established duration of stability at -60 to -80°C of 16 weeks. Of the incurred samples that were reanalyzed, 67% of these samples yielded concentrations that were within 30% of the initial analysis. Based on the results, the assay's performance has been shown to be acceptable for measurement of ansuvimab-zykl in the serum of uninfected NHP.

Measurement of Ansuvimab-zykl in Serum of Infected NHPs

Not applicable. Ansuvimab-zykl concentrations were not quantified in EBOV-infected NHPs.

15. Trial Design: Additional Information and Assessment

15.1. The PAmoja TuLinde Maisha Study: NIH 19-I-0003 Protocol

Note: The protocol synopsis was provided by the Applicant. Cross-references in this section are therefore not consistent with the remainder of the review.

1. Protocol Overview and Conduct

Applicant:	Ridgeback Biotherapeutics, LP.
Drug Name:	Ebanga (ansuvimab-zykl) *referred to as ansuvimab-zykl or mAb114 in this document*
Indication:	For the treatment of infection caused by *Zaire ebolavirus* in adult and pediatric patients, including neonates born to a mother who is reverse transcriptase polymerase chain reaction (RT-PCR) positive for *Zaire ebolavirus* infection.

Protocol Title:	The PAmoja TuLinde Maisha (PALM) study: A Multicenter, Multi-Outbreak, Randomized, Controlled Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with Ebola Virus Disease
Source of Information:	• 19-I-0003 Protocol V7.0, dated October 4, 2019 * • Statistical Analysis Plan for PALM RCT Extension Phase V1.0 dated August 21, 2020 * • Statistical Analysis Plan for IND # 138090: A Focused Assessment of Two Treatments from NIH Protocol: 19-I-0003 (IND #: 125530), v.2, February 14, 2020 * Each of the documents listed above were prepared by and provided by the NIH, NIAID
IND sponsor/Study Sponsor:	Office of Clinical Research Policy and Regulatory Operations (OCRPRO) National Institute of Allergy and Infectious Diseases 5601 Fishers Lane Bethesda, MD 20892 Study drug provided by Ridgeback Biotherapeutics, L.P.
Trial Identifiers	
Protocol Number:	19-I-0003
Clinical Phase:	2/3
EudraCT Number:	Not applicable (performed in Democratic Republic of Congo)
Other Codes:	Not applicable
IND Number:	125530
ClinicalTrial.gov identifier:	NCT03719586
Ethics:	The protocol, associated materials, and modifications have been submitted to an Independent Ethics Committee and Institutional Review Board operating in compliance with current regulations of ICH E6. The IRB name and address are: (b) (4)
Trial Centers:	Four centers in the DRC: Beni, Butembo, Katwa, and Mangina

1.1. Design

Planned duration of main phase:	Start Date: November 2018 End Date: November 2023 (i.e., nominally up to 5 years, but could be shortened or lengthened depending upon the pace of subsequent outbreaks in order to reach desired sample size) On August 9, 2019, the DSMB recommended stopping the PALM RCT and made a recommendation for an extension phase to continue with randomization to the ansuvimab-zykl or REGN-EB3 arms of the study. These recommendations were based on an interim analysis of 499 participants enrolled into the RCT, which revealed that ansuvimab-zykl was close to crossing an early monitoring boundary for efficacy over ZMapp. The DSMB also noted that REGN-EB3 crossed an early monitoring boundary for efficacy relative to ZMapp. Furthermore, the mortality rates for ansuvimab-zykl and REGN-EB3 were not statistically significantly different, justifying the continued randomization to these two therapies.
Trial Status	Ongoing.
Date of Database lock:	January 17, 2020 for the Main Phase of the study
Other Important Dates	August 9, 2019 (Main phase of trial stopped based on recommendation of Data Safety Monitoring Board).

1.2. Objectives

A streamlined set of data elements will be collected that represents a pared-down version of data collected during the formal PALM RCT to minimize the burden to the sites.

1.2.1. Primary Objective

- To summarize 28-day mortality in patients with Ebola virus disease who receive ansuvimab-zykl or REGN-EB3

1.2.2. Secondary Objective

- To summarize the safety and tolerability of ansuvimab-zykl and REG-EB3
- To evaluate the effect of baseline characteristics, including age, sex, CtNP, days from onset of illness to treatment, self-reported rVSV vaccination, baseline blood chemistries, and clinical information by treatment arm
- To summarize time to death of participants by treatment arm

- To compare the mortality rates of subjects treated with ansuvimab-zykl relative to ZMapp up to 58 days after randomization
- To compare time to successful discharge from the Ebola treatment unit (ETU) for subjects treated with ansuvimab-zykl relative to ZMapp
- To compare time to first negative Ebola virus RT-PCR results in the blood from subjects treated with ansuvimab-zykl relative to ZMapp
- To compare time to two consecutive negative Ebola virus RT-PCR results in the blood from subjects treated with ansuvimab-zykl relative to ZMapp

1.2.3. Exploratory Objectives

- To evaluate differences in mortality rates by treatment arm between the primary PALM phase and the Extension phase.

1.3. Selection of Trial Population

In addition to the inclusion and exclusion criteria provided below, the following key points about pregnant women and children and neonates should be noted:

- Although a full understanding of the potential risks from the study medications to human fetuses was lacking, given the mortality associated with Ebola virus infection and the likelihood that there is a greater risk to the fetus from severe *Zaire ebolavirus* infection than from the study medications themselves, pregnant women were permitted entry into the study.
- Although study medications had only been tested in limited fashion, or not at all, in children, children of any age were eligible for enrollment given the likelihood that untreated Ebola infection may pose greater risk than exposure to the study medications. Neonates (defined as ≤7 days old) born to a mother who was RT-PCR positive for acute Ebola virus were presumed to be RT-PCR positive for acute Ebola virus at delivery and were eligible for enrollment even prior to RT-PCR confirmation (i.e., obtaining those results could pose unnecessary delay).

1.3.1. Key Inclusion Criteria

- Males or females of any age with documented positive RT-PCR in blood for acute Ebola virus infection within 3 days prior to enrollment and who have symptoms of any duration (see special provision for neonates).
  - A neonate (defined as ≤7 days old) born to a mother who is RT-PCR positive for acute Ebola virus represents a special case. These neonates are presumed to be RT-PCR positive for acute Ebola virus at delivery, with untreated infection posing a greater risk than exposure to study medication. As such, neonates born to an infected mother who has not yet cleared the Ebola virus are eligible for enrollment even prior to RT-PCR confirmation (i.e., obtaining those results could pose unnecessary delay). Neonates born to a mother who has cleared Ebola virus following a course of her assigned investigational medication may be enrolled prior to RT-PCR confirmation according to the discretion of the investigator regarding the likelihood that the neonate is infected (e.g., based on the interval between when the mother clears the virus and the baby is born).

- Willingness of study participant to accept randomization to any assigned treatment arm.
- All males and females of childbearing potential must be willing to use effective methods of contraception, from time of enrollment until Day 58 of study.
- Must agree not to enroll in another study of an investigational agent prior to completion of Day 28 of study.
- Ability to provide informed consent personally, or by a legally acceptable representative if the patient is unable to do so.

1.3.2. Key Exclusion Criteria

- Patients who, in the judgment of the investigator, will be unlikely or unable to comply with the requirements of this protocol through Day 28.
- Prior treatment with any investigational antiviral drug therapy against Ebola virus infection within 5 half-lives or 30 days, whichever is longer, prior to enrollment. Patients who have received a licensed immunization against Ebola virus remain eligible.

1.4. Hypotheses

No formal hypothesis tests are planned.

1.5. Treatment Groups

- Ansuvimab-zykl (Ebanga) plus optimized standard of care (oSOC)
- REGN-EB3 (Inmazeb) plus oSOC

Randomization takes place on a 1:1 basis.

Randomization will be stratified by RT-PCR cycle threshold (CT), ETU, and outbreak. Cycle thresholds can be calculated using glycoprotein gene targets (gpCT) or nucleoprotein gene targets (CtNP). This study will use CtNP for stratification (CtNP $\leq$22.0 versus CtNP >22.0).

1.6. Endpoints and Definitions

Study endpoints will be evaluated by comparing randomized groups.

Primary Endpoint

- 28-day mortality

Secondary Endpoints

- Incidence of serious adverse events (SAEs; see safety section for limitations on collection)
- Incidence of infusion-related adverse reactions

1.7. Interim Analysis

Interim monitoring was prespecified in the protocol, to introduce new arms and allow early stopping for futility, efficacy, or safety.

Per protocol, interim monitoring used symmetric upper and lower boundaries for comparisons of a given arm to the control. The O'Brien-Fleming alpha-spending procedure will truncate

boundaries at a one-sided type I error rate of 0.001. Four interim looks (including the final analysis) were planned, roughly corresponding to endpoint data from 33, 65, 100, and full enrollment (170 REGN-EB3 and 185 in each of the other three arms). The upper boundaries for the z-scores at these looks are 3.09, 3.09, 3.09, and 1.98. The protocol acknowledged that the timing of analyses might change depending on the size of the outbreak.

On August 9, 2019, the DSMB recommended stopping the PALM RCT before the planned enrollment (725 patients) was met and also recommended the Extension Phase commence with only REGN-EB3 and ansuvimab-zykl. These recommendations were based on interim analysis of 499 participants enrolled into the PALM RCT with at least 10 days of follow-up, which revealed that REGN-EB3 crossed prespecified boundary for efficacy over ZMapp. Mortality rates in the REGN-EB3 and ansuvimab-zykl treatment groups were similar, and both were lower than ZMapp (control group) and remdesivir groups. Thus, the DSMB recommended that the PALM RCT continue into an Extension Phase and randomize patients to either REGNEB3 or ansuvimab-zykl to evaluate safety.

Since the study stopped early, after the fourth interim analysis, the final assessment of significance was conservatively made using the 5th interim monitoring boundary. Thus, a p-value <0.028 (2-sided) for the comparison of REGN-EB3 versus ZMapp at the final analysis was required to claim statistical significance for primary endpoint.

1.8. Data Monitoring Committee

An independent DSMB with international representation of the host countries participating in the trial will review the study no less than twice a year. The DSMB may convene additional reviews as necessary, dependent on the rate of subject accrual. The DSMB will review the study data to evaluate the safety, efficacy, study progress, and conduct of the study. All SAEs, all unanticipated problems, and all IND Safety Reports will be reported by the Data Coordinating Center to the DSMB at the same time they are submitted to the IRB or IND Sponsor. The Principal Investigator will submit the DSMB's written summary open reports with the DSMB's recommendations to the IRB. A specific DSMB charter will be put in place establishing the roles and responsibilities of members after review and approval by the Study Steering Committee.

- The DSMB will monitor safety, efficacy, and quality of trial conduct measures closely throughout the trial and may pause enrollment in the event of unanticipated study-related deaths or SAEs that are considered study-related.
- The DSMB will also review the completeness of follow-up and other aspects of study conduct.
- After each meeting they will recommend that the study be continued as planned, modified, or terminated.

1.9. Endpoint Adjudication Committee

Not applicable.

1.10. Sample Size Considerations

1.10.1. Sample Size Assumptions

The study initially targeted 125 patients per group based on an expected 28-day mortality rate of 30% in the ZMapp group, with a 50% relative reduction in the experimental treatment (i.e., rate of 15%). On July 17, 2019, a letter of amendment was submitted to the NIAID and DRC ethics boards requesting to enlarge the sample size to 725 to increase power and allow for a smaller, clinically meaningful treatment effect than the original assumed 50% decrease in mortality from 30% (control) to 15% (new investigational product). Since REGN-EB3 was not included until amendment 3, the planned enrollment was 170 on REGN-EB3 versus 185 in each of the other treatment groups.

1.10.2. Rationale for NI Margin

Not applicable as this was a superiority study design.

1.10.3. Response Rate Assumptions

Not applicable.

1.11. Analysis Populations

The overall intent-to-treat population (oITT) includes all patients who were randomized to one of the two treatment arms, regardless if they actually received treatment. All tables using the oITT population will group and summarize patients according to the treatment to which they were originally randomized or subsequently randomized for those during the quarantine.

The treated population includes all oITT patients who actually received drug. Patients will be grouped based on the drug actually, initially received. This group will be used to assess sensitivity to incorrect randomizations and switched treatments.

The concurrent intent-to-treat (cITT) population includes all patients in the oITT except those who were subsequently randomized to another drug when the original drug was either unavailable or quarantined.

The amended randomization population includes all subjects in the cITT population who completed all doses of assigned study product and did not have one of the following protocol deviations:

- Subjects who were randomized as part of the original 3-arm study are excluded (randomized prior to December 2018 amendment). Prior to this amendment 15 subjects were randomized to ZMapp, 17 subjects to ansuvimab-zykl, and 18 subjects to remdesivir.
- Subjects who were originally randomized to ZMapp but where ZMapp was unavailable due to a drug shortage or quarantine, are excluded.
- Subjects who were originally randomized to ZMapp but were re-randomized to another investigational treatment after the ZMapp treatment was terminated, are excluded.
- Subjects who received immunization against Ebola virus within 30 days of first dose are excluded since the effect of vaccine on effectiveness of treatments is unknown. Tables

utilizing the amended randomization analysis population group subjects according to the treatment they actually received.

The safety population includes all subjects who received at least one dose of medication.

1.12. Time Point Description

The primary endpoint was 28-day mortality. Patients were followed to Day 58. Viral load measurements were collected at admission to the ETU and on days 1, 2, 3, 4, 5, 6, 8, 10, 14, and 28. Follow-up viral load measurements were not systematically provided.

1.13. Analysis Description

1.13.1. Analysis of Primary Outcome

The primary efficacy analysis of 28-day mortality rate was compared between ansuvimab-zykl and ZMapp using Boschloo's test for participants who were concurrently randomized (intent-to-treat concurrent analysis set). The 2-sided p-value was obtained by the Boschloo's test, and statistical significance was claimed if the 2-sided p-value was less than the monitoring boundary allocating a total type I error rate of 0.05 across interim analyses. Corresponding 95% confidence intervals were calculated.

For the overall study, the type I error rate was controlled at the 5% level. Interim monitoring boundaries were established using a truncated O'Brien-Fleming boundary. Since the study stopped early, after the fourth interim analysis, the final assessment of significance was conservatively made using the 5th interim monitoring boundary. Thus, a p-value<0.028 (2-sided) for the comparison of ansuvimab-zykl versus ZMapp at the final analysis was required to claim statistical significance for the primary endpoint. A missing value for 28-day mortality was imputed as death.

1.13.2. Secondary Outcomes and Analyses

1.13.2.1. Evaluating Safety and Tolerability

Safety will be evaluated by computing the proportion of patients with at least one SAE in each arm. Proportions of specific SAEs, to include infusion-related events, will be reported for each study arm. Clopper-Pearson confidence intervals for within-arm proportions will be presented. Differences in SAE proportions between arms will be computed along with 95% confidence intervals.

Table: Number (%) of patients with at least one SAE for each study arm, with 95% confidence intervals.

List of SAEs: Randomized arm, days from randomization to first SAE experienced by a subject, subject ID, site, age, days from start of study drug to SAE, SAE (MedDRA system organ class and preferred term, and verbatim description), severity grade, relatedness to study intervention, outcome (sort by randomized arm, subject ID, MedDRA system organ class and preferred term and, if a subject has multiple SAEs, days from randomization to SAE).

1.13.2.2. Evaluating the Effect of Baseline Characteristics on Mortality

Univariate and multivariate logistic regressions will evaluate the association of baseline characteristics with 28-day mortality (1 = death, 0 = survival). Predictor variables include selected baseline characteristics as follows:

- Age
- Sex
- Weight
- Blood pressure
- Pulse
- Body temperature
- Respiratory rate
- Oxygen saturation
- CtNP
- CtGP
- CtNP ≤22 versus >22
- Creatinine
- Potassium
- Sodium
- Aspartate aminotransferase (AST)/SGOT
- Alanine aminotransferase (ALT)/SGPT
- Self-report rVSV vaccination status
- Date of self-reported rVSV vaccination <10 days versus ≥10 days prior to screening
- Days from self-reported onset of symptoms to screening
- Days from self-reported onset of symptoms to study agent administration
- Positive result for malaria

1.13.3. Sensitivity and Supportive Statistical Analyses Description

Logistic regressions were used to assess the impact of covariates on 28-day mortality. The covariates included CtNP category, age, Ebola vaccination status, ETU, and sex. Sensitivity analyses were performed using the same statistical method in different analysis sets, including the oITT, treated population, and the amended randomization population.

1.13.3.1. Other Efficacy Analysis

Not applicable.

1.13.3.2. Safety Analysis

Refer to Section 1.13.2.1

1.13.3.3. Viral Genotyping/Phenotyping Analyses

Viral load analysis will not be possible during the extension phase, as the protocol was simplified such that regular viral load measurements were not recorded. The presence of Ebola viral RNA in semen is also not possible as samples were not collected during the extension phase. Please refer to 1.5.

1.13.3.4. Pharmacokinetic Analyses

Not applicable.

1.13.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

1.13.3.6. Health Outcomes Analyses

Comparison of mortality rates among patients whose baseline predictors of disease place them in high risk versus low risk categories for disease severity may be conducted using variables collected during the extension phase, with the combined main phase and extension data.

1.13.4. Changes in Conduct of the Study or Planned Analyses

No further changes in conduct of the study or planned analyses are anticipated at this time.

15.2. MEURI Expanded Access Protocol

Note: The protocol synopsis was provided by the Applicant. Cross-references in this section are therefore not consistent with the remainder of the review.

1. Protocol Overview and Conduct

Applicant:	Ridgeback Biotherapeutics, LP.
Drug Name:	Ebanga (ansuvimab-zykl) *referred to as ansuvimab-zykl or mAb114 in this document*
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.
Protocol Title:	Open-label, expanded access protocol of a human monoclonal antibody, ansuvimab-zykl (mAb114), administered as an investigational therapeutic to Ebola infected patients or as a high-risk Ebola postexposure prophylaxis
Source of Information:	• MEURI EAP Version 2.0 Dated November 2, 2020 • Study is sponsored by INRB; study drug is provided by Ridgeback Biotherapeutics, L.P.
Trial Identifiers	
Protocol Number:	MEURI EAP-2020-EP-DRC-INRB

Clinical Phase:	Expanded Access / Compassionate Use Study
EudraCT Number:	Expanded Access / Compassionate Use Study
Other Codes:	MEURI EAP
IND Number:	138090
ClinicalTrial.gov identifier:	N/A (performed in Democratic Republic of Congo)
Ethics:	Institutional Review Board and Ethics Committee
Trial Centers:	Medicines Sans Frontier, World Health Organization (WHO)/Ministry of Health, Alliance for International Medical Action, Samaritan's Purse, International Medical Corps

1.1. Design

Planned duration of main phase:	Unknown at this time; Open in response to active *Zaire ebolavirus* outbreak
Planned duration of extension phase:	Survivors will be enrolled in a follow-up program to be coordinated by the Ministry of Health in DRC and the WHO. In addition, for any pregnant women who receive treatment, every attempt will be made by the protocol study team (PST) to track the pregnancy through delivery to determine the outcome.
Trial Status	Ongoing.
Date of Database lock:	Not yet determined; study remains ongoing in response to active *Zaire ebolavirus* outbreak
Other Important Dates	N/A

1.2. Objectives

1.2.1. Primary Objective

- To treat patients with *Zaire ebolavirus* infection with ansuvimab-zykl
- To treat subjects who had a high-risk exposure to EBOV with ansuvimab-zykl as postexposure prophylaxis (PEP)

1.2.2. Secondary Objective

- To collect basic outcomes data including documentation of any hypersensitivity reactions, self- reported adverse events (AEs) and survival data
- To assess ansuvimab-zykl pharmacokinetics in patients with *Zaire ebolavirus* infection, especially in patients with high viral load and fatal outcome
- To quantify sGP in patients with *Zaire ebolavirus* infection receiving ansuvimab-zykl

1.2.3. Exploratory Objectives

None

1.3. Selection of Trial Population

This protocol is designed for the participation of *Zaire ebolavirus*-infected children and adults.

All patients must also receive local optimized standard of care, potentially including but not limited to: IV fluids, antipyretics, and electrolyte replacement.

Participants with recent high-risk EBOV exposure, as determined by study clinicians, can also be treated with ansuvimab-zykl for PEP. A potential patient and an event of exposure should be assessed by a qualified clinician and determined to be consistent with a high-risk exposure. The *WHO Notes on Ebola Postexposure Prophylaxis for Frontline Healthcare Workers* may be used as guidance. While many potential exposures could be considered high-risk, the following are *examples* of potential high-risk EBOV exposures:

- Needlestick injury in ETU
- Direct contact with body fluids from a patient with *Zaire ebolavirus* infection
- Close contact with patient with *Zaire ebolavirus* infection without personal protective equipment.

For documented cases of high-risk EBOV exposure, ansuvimab-zykl treatment should be initiated at the earliest possible time, preferably within 72 hours of exposure.

Newborn babies of mothers with confirmed *Zaire ebolavirus* infection are eligible for PEP and can be treated with ansuvimab-zykl based on clinical judgement.

WHO Notes on Ebola Postexposure Prophylaxis for Frontline Healthcare Workers: concurrent administration of an Ebola vaccine and an antibody-based therapeutic is not recommended. Individuals who received an Ebola vaccine ≥10 days or more prior to exposure are expected to have good protection from the vaccine and may not need PEP.

1.3.1. Key Inclusion Criteria

A patient must meet all the following criteria:

- Male or female with laboratory confirmed (based on local standard of care) EBOV infection or with recent high-risk EBOV exposure as determined by a treating physician or designee.
- Able to provide proof of identity to the satisfaction of the clinical team.
- Able and willing to complete the informed consent process personally, or if the patient is unable to do so, then informed consent completed by a legally-authorized representative according to local laws and regulations.
  - Please note that there is no distinct Parent/Guardian informed consent form used for this study; instead the Assent Form concludes with an instruction to parents/guardians to complete the (adult) informed consent form.

1.3.2. Key Exclusion Criteria

Any medical condition that, in the opinion of the treating physician, would place the patient at an unreasonably increased risk through participation in this treatment protocol.

1.4. Hypotheses

As an open-label, expanded access program, this study did not seek out to explicitly test a given hypothesis.

1.5. Treatment Groups

Ansuvimab-zykl administered as a single IV infusion of 50 mg/kg.

1.6. Endpoints and Definitions

As an EAP, this study does not have a primary endpoint. Secondary endpoints include:

- Survival of patients
- Tabulation of SAEs and AEs that by clinical judgement are atypical for *Zaire ebolavirus* infection
- Tabulation of infusion related AEs
- Levels of viral load

1.7. Interim Analysis

There is no planned interim analysis in this study.

A protocol study team will meet to communicate about study progress and perform ongoing safety data reviews on a regular basis. Composed of the prescribing information, other study clinicians, and the IND medical officer, the PST will review the summary study safety data reports as they become available through 3 weeks after the last subject receives the study product. In addition, the PST will meet to evaluate and respond in a timely manner to any individual serious AEs or new patterns in aggregate AEs that may arise in relation to the events described in the current product labeling (package insert or Investigator's Brochure).

1.8. Data Monitoring Committee

If possible, site investigators will allow the study monitors, the IRB/EC, the US FDA, and the DRC regulatory authorities to inspect study documents (e.g., consent forms, drug distribution forms, case report forms) and pertinent hospital or clinic records for confirmation of the study data.

Copies of documents could be requested if access to originals is not available in the outbreak.

1.9. Endpoint Adjudication Committee

Not applicable.

1.10. Sample Size Considerations

Not applicable in an EAP.

1.10.1. Sample Size Assumptions

Not applicable.

1.10.2. Rationale for NI Margin

Not applicable.

1.10.3. Response Rate Assumptions

Not applicable.

1.11. Analysis Population and Time Point Description

The analysis population will include all patients with available data.

1.12. Analysis Description

1.12.1. Primary Efficacy Analysis Description

Not applicable in an EAP.

1.12.2. Sensitivity and Supportive Statistical Analyses Description

1.12.2.1. Other Efficacy Analysis

The proportion of patients who died will be summarized by the following:

- Sex: Male, Female
- Age Category 1: <18 years old, ≥18 years old
- Age Category 2: <5 years, 6 to 12 years, 13 to 17 years, ≥18 years
- CtNP category: ≤22 CtNP, >22 CtNP
- ETU
- Treatment start relative to onset: ≤5 days of onset versus >5 days from onset

Graphically, a Kaplan-Meier (KM) plot of time-to-discharge from the ETU will be presented as well as summary statistics for mean, SD, and KM estimate of median. Patients who died prior to

discharge will be censored at the day of death. Patients ongoing at the time of the data cut will be censored.

For those patients who died, the time from treatment start to death will be summarized and graphically displayed in a KM plot. Patients who were discharged from ETU will be censored at the date of discharge.

Times from onset of disease to admission into ETU and to treatment start will be summarized overall and by the following:

- Sex: Male, Female
- Age Category 1: <18 years old, ≥18 years old
- Age Category 2: <5 years, 6 to 12 years, 13 to 17 years, ≥18 years
- CtNP category: ≤22 CtNP, >22 CtNP
- ETU

1.12.2.2. Safety Analysis

Subjects will be followed for up to 3 weeks after the product administration or until discharge from the ETU, whichever is later. Survival status for infected patients and/or *Zaire ebolavirus* disease status for PEP subjects will be recorded as applicable.

Assessments of safety will include clinical observation and monitoring following administration. Patients will be monitored and assessed daily through discharge for safety and the incidence of serious adverse events and AEs that by clinical judgement are atypical for *Zaire ebolavirus* infection, and any AEs that occur during product infusions.

1.12.2.3. Viral Genotyping/Phenotyping Analyses

Blood will be collected for ansuvimab-zykl PK assessment, sGP quantification, and RT- PCR evaluation of viral load by available assay. A blood sample for Ebolavirus viral load measurement is collected before ansuvimab-zykl administration and at subsequent study timepoints. The GeneXpert Ebola Assay, approved for Emergency Use Authorization from WHO and FDA, will be used for detection of the EBOV RNAs encoding surface GP and NP. The quantification of sGP will be performed and summarized from samples taken at baseline, at 30 minutes after the end of infusion, between Days 2 and 3, between Days 7 and 10, and between Days 14 and 21.

1.12.2.4. Pharmacokinetic Analyses

For the PK study, ansuvimab-zykl serum concentration data will be summarized for samples collected per the following schedule:

- The first sample collection timepoint must be taken within no more than 30 minutes after the end of the infusion (a predose sample can be collected (optional), but it is not mandatory). The sample should be collected from the arm distal to or opposite of the arm with the IV infusion line.
- The second sample collection timepoint should be taken between Days 2 and 3, at any time within the 24 hours between Days 2 and 3, or within 48 to 72 hours of the end of the IV infusion.

- The third sample collection timepoint should be taken between Days 7 and 10, with an emphasis on collection in the latter portion of this defined window, if available.
- The fourth sample collection timepoint should be taken between Days 14 and 21, at any time within the 7 days occurring between Days 14 and 21.
- A fifth sample collection timepoint at the survivor follow-up visit (a month after discharge) is also desirable, if available.

For adequate analysis of the PK, the analysis dataset will need to include results from at least 30 patients, where at least 50% of those sampled are survivors.

If previous PK models are available, fewer patients (20 patients) and fewer time points can be used in the analysis dataset.

1.12.2.5. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic analyses will be performed using data from the analysis of patient samples at timepoints identified in the Schedule of Evaluations for the study (Protocol version 2.0 dated November 2, 2020, Appendix III). A copy of the Schedule of Evaluations is provided here for ease of review as Table 1 below.

Pharmacokinetic analysis of the ansuvimab-zykl concentration will be performed using both compartmental and noncompartmental approaches. C_{max} and time of maximum concentration will be taken directly from the observed concentration–time data.

1.12.2.6. Health Outcomes Analyses

Not applicable.

1.12.3. Changes in Conduct of the Study or Planned Analyses

Since the initiation of the study, and at the suggestion of FDA, Ridgeback added the collection of patient blood samples for later pharmacokinetic and sGP analysis. No further changes in conduct of the study or planned analyses are anticipated at this time.

Table 45. Schedule of Evaluations in MEURI-EAP-2020-EP-DRC-INRB (v.2, November 2, 2020)

Schedule of Evaluations							
Visit number	01	02	03	04	05	06	07
Time after day 0 infusion, days		1-2	2-3	7-10	14-21	21	21+N
Day on protocol	D0	D1	D2	D7	D14	D21	S
Informed consent	X						
Study product administration	X						
Plasma sample collection for viral load[a]	X	X		O	O	O	O
Serum sample collection for ansuvimab-zykl PK and sGP quantification	Y1		Y2	Y3	Y4		Y5
Limited medical exam, safety evaluation	X	X		X	X	X	X
Administration site evaluation	X	X		X			

[a] One (1) EDTA tube of blood collected before product administration on Day 0 and 1 EDTA tube between 24 to 72 hours following product administration for viral load measurement. Plasma should be separated and used as per available PCR assay requirements. If poss ble, some plasma should be kept frozen in aliquots in case the assay has to be repeated.
N – Any follow-up visit subsequent to D21 (i.e., period is not fixed as it applies to patients who received ansuvimab-zykl as PEP, as well as for therapeutic treatment under this protocol).
D – Study day
S – Survival data
X – Sample is required at the designated timepoint
O – Sample should be collected whenever clinically feasible.
Y – Sample is required at designated timepoint as follows:

1. One optional serum separator tube (SST) of blood collected before product administration on Day 0 (pre dose) and another SST collected within 30 min after the end of infusion.
2. One SST of blood collected at D2 or 3 (any time within the 24 hours between D2 and 3).
3. One SST of blood collected between D7 and 10 (as late as possible within this time frame).
4. One SST of blood collected between D14 and 21. This timepoint will be the last for sGP quantification.
5. One SST of blood collected at the survivor follow-up visit one month after discharge from ETU is also desirable, if available.

16. Efficacy: Additional Information and Assessment

16.1. Additional Analyses of Demographics

This section supplements the analyses and interpretation presented in Section 6.2.4.1. The baseline vital signs such as temperature, systolic and diastolic blood pressure, pulse, respiratory rate, and oxygen saturation, were similar between the two arms (Table 46).

Table 46. Summary of Baseline Vital Signs, Concurrent ITT Population, PALM Trial

Subgroup	Ansuvimab-zykl	ZMapp	Total
Concurrent ITT			
N	174	168	342
Baseline weight (kg)			
n	174	168	342
Mean (SE)	44.9 (1.51)	49.2 (1.49)	47.0 (1.06)
Median	50	52	51
Range	(3, 93)	(2, 100)	(2, 100)
SD	19.86	19.25	19.66

Subgroup	Ansuvimab-zykl	ZMapp	Total
Baseline oxygen saturation (%)			
n	168	165	333
Mean (SE)	95.4 (0.39)	95.1 (0.32)	95.3 (0.25)
Median	96	96	96
Range	(56, 100)	(69, 100)	(56, 100)
SD	5.1	4.1	4.6
Baseline respiratory rate (breaths/min)			
n	170	166	336
Mean (SE)	26.0 (0.58)	25.8 (0.62)	25.9 (0.42)
Median	24	24	24
Range	(18, 63)	(16, 64)	(16, 64)
SD	7.5	8.0	7.7
Baseline diastolic blood pressure			
n	152	159	311
Mean (SE)	68.2 (1.2)	70.2 (1.2)	69.24 (0.8)
Median	66	68	67
Range	(36, 127)	(41, 125)	(36, 127)
SD	14.2	14.6	14.4
Baseline systolic blood pressure			
n	152	159	311
Mean (SE)	107.1 (1.5)	109.0 (1.5)	108.1 (1.0)
Median	105	107	106
Range	(51, 171)	(72, 179)	(51, 179)
SD	18.1	18.4	18.3
Baseline temperature			
n	173	168	341
Mean (SE)	37.33 (0.09)	37.56 (0.09)	37.45 (0.07)
Median	37.2	37.7	37.4
Range	(34.4, 40.4)	(35.2, 40.7)	(34.4, 40.7)
SD	1.22	1.17	1.20
Baseline pulse (beats/min)			
n	172	168	340
Mean (SE)	97.5 (1.6)	96.7 (1.7)	97.1 (1.16)
Median	97.5	94.5	96.0
Range	(53, 150)	(47, 162)	(47, 162)
SD	20.4	22.4	21.4

Source: from Statistical reviewer, ADSL and SAS software used
Abbreviations: ITT, intent-to-treat; PALM, PAmoja TuLinde Maisha

16.2. Additional Analyses for the Primary Efficacy Endpoint

This section supplements the analyses and interpretation presented in Section 6.2.4.2. Detailed information on the subjects excluded from the concurrent ITT analysis population and the two concurrent ITT sensitivity analysis populations are presented here.

16.2.1. Subjects Excluded From the Concurrent ITT Population for the Primary Efficacy Analysis

The drug-shortage periods that occurred during the PALM Trial are listed in Table 47. There were 11 subjects randomized during three drug shortage periods. Only subjects who received either ansuvimab-zykl or ZMapp are considered in the BLA, and thus this BLA included four

subjects, (b) (6) who received either ansuvimab-zykl or ZMapp when some investigational drugs were not available. Two subjects, (b) (6) were rerandomized. Subject (b) (6) was randomized to the ZMapp arm during a shipment delay. This subject was rerandomized to ZMapp again. Because the site decided to wait for the assigned drug, subject (b) (6) was included in the concurrent ITT population. The other three subjects, (b) (6) were excluded from the concurrent ITT population. A summary of how these subjects differed between analysis populations is provided in Table 48.

Table 47. Drug Shortage Periods in the PALM Trial

Drug Shortage Period	Drug Not Available	Subject ID	Original Randomized Treatment Assignment	Treatment Assignment From Rerandomization	Actual Treatment Received
1/23/2019 to 2/4/2019	ZMapp	(b) (6)	REGN-EB3		REGN-EB3
			Remdesivir		Remdesivir
			ZMapp	REGN-EB3	REGN-EB3
			ansuvimab-zykl		ansuvimab-zykl
			Remdesivir		Remdesivir
			ansuvimab-zykl		ansuvimab-zykl
			REGN-EB3		REGN-EB3
3/28/2019	ZMapp		REGN-EB3	---	REGN-EB3
			REGN-EB3	---	REGN-EB3
			ZMapp	ZMapp	ZMapp
5/2/2019 10:30 AM to 1:40 PM	REGN-EB3		REGN-EB3	ZMapp	ZMapp

Source: reviewer analysis of the Randomization Quality Control Report, Data Handling Report, Listing 16.1.7.1 and DS dataset.
Abbreviations: PALM, PAmoja TuLinde Maisha

Table 48. Subjects Who Differed Between Analysis Populations

Subject ID	Final Randomized Assignment	Actual Treatment Received	Concurrent ITT	Treated	Safety
(b) (6)	ansuvimab-zykl	ansuvimab-zykl	No	Yes	Yes
	ansuvimab-zykl	ansuvimab-zykl	No	Yes	Yes
	ZMapp	ZMapp	Yes	Yes	Yes
	ZMapp	ZMapp	No	Yes	Yes

Source: from Statistical reviewer, assembled from the materials submitted.
Abbreviations: ITT, intent-to-treat; Treated, all patients treated

16.2.2. Sensitivity Analyses Populations for Primary Efficacy Endpoint

Two concurrent ITT sensitivity analysis populations were generated by the reviewer. The first, cITT2, is the concurrent ITT population with exclusion of 32 subjects who were randomized before January 26, 2019. These 32 subjects consist of the not cITT2 analysis population.

The second cITT3 is the concurrent ITT population with exclusion of six subjects, (b) (6) who received ZMapp and were rerandomized to receive either REGN-EB3 or ansuvimab-zykl after the trial was stopped and the extension phase began (Table 49).

Table 49. Eleven Subjects Who Were Rerandomized After Cessation of the PALM Trial

Subject ID	Original Randomized	Rerandomization After August 9, 2019 DSMB Decision	Included in Analysis Population Under Treatment		
			Overall ITT	Concurrent ITT	Concurrent ITT Sensitivity 3
(b) (6)	ZMapp	REGN-EB3	ZMapp	ZMapp	No
	Remdesivir	ansuvimab-zykl	No	No	No
	ZMapp	ansuvimab-zykl	ZMapp	ZMapp	No
	ansuvimab-zykl	REGN-EB3	No	No	No
	ZMapp	ansuvimab-zykl	ZMapp	ZMapp	No
	ZMapp	REGN-EB3	ZMapp	ZMapp	No
	Remdesivir	ansuvimab-zykl	No	No	No
	Remdesivir	ansuvimab-zykl	No	No	No
	ZMapp	ansuvimab-zykl	ZMapp	ZMapp	No
	Remdesivir	REGN-EB3	No	No	No
	ZMapp	ansuvimab-zykl	ZMapp	ZMapp	No

Source: Statistical reviewer; assembled from the materials submitted.
Abbreviations: DSMB, data safety monitoring board; ITT, intent-to-treat; mAb, monoclonal antibody; PALM, PAmoja TuLinde Maisha

The time from randomization to switch to a new treatment by rerandomization was 3 to 8 days for these six subjects, who received one to three doses of ZMapp (Table 50). Among those six subjects, only one died (on study Day 6); the others survived to Day 58.

Table 50. Subjects Who Received ZMapp But Were Rerandomized After the Interim Analysis, PALM Trial

Subject ID	Site	CtNP	Original Treatment	# of Doses Received	# of Days at Switch	New Treatment	Death?	End of Study Day
(b) (6)	Beni	>22	ZMapp	2	7	REGN-EB3		58
	Beni	>22	ZMapp	1	4	REGN-EB3		57
	Beni	>22	ZMapp	2	6	ansuvimab-zykl		59
	Beni	>22	ZMapp	2	5	ansuvimab-zykl		57
	Mangina	>22	ZMapp	3	8	ansuvimab-zykl		59
	Mangina	≤22	ZMapp	1	3	ansuvimab-zykl	Death	6

Source: Statistical reviewer; ADSL and SAS software used.
Abbreviations: CtNP, cycle-threshold nucleoprotein gene targets; mAb, monoclonal ant body; PALM, PAmoja TuLinde Maisha

16.3. Additional Analyses for Secondary Analyses

This section supplements the analyses and interpretation presented in Section 6.2.4.2 with additional secondary efficacy analyses: discharge by study day and the Kaplan-Meier curve for the probability of survival.

Discharge From Ebola Treatment Unit by Study Day

A summary of death or discharge from the ETU is provided in Table 51. Subjects were discharged from the ETU as early as Day 1 and Day 5 for ansuvimab-zykl and ZMapp, respectively. Most subjects were discharged on Day 16 or Day 17. In total, by Day 28, 104 subjects (60%) in ansuvimab-zykl and 77 subjects (46%) in ZMapp were discharged from the ETU.

Table 51. Summary of Death and Discharge From ETU by Study Day, Concurrent ITT Population, PALM Trial

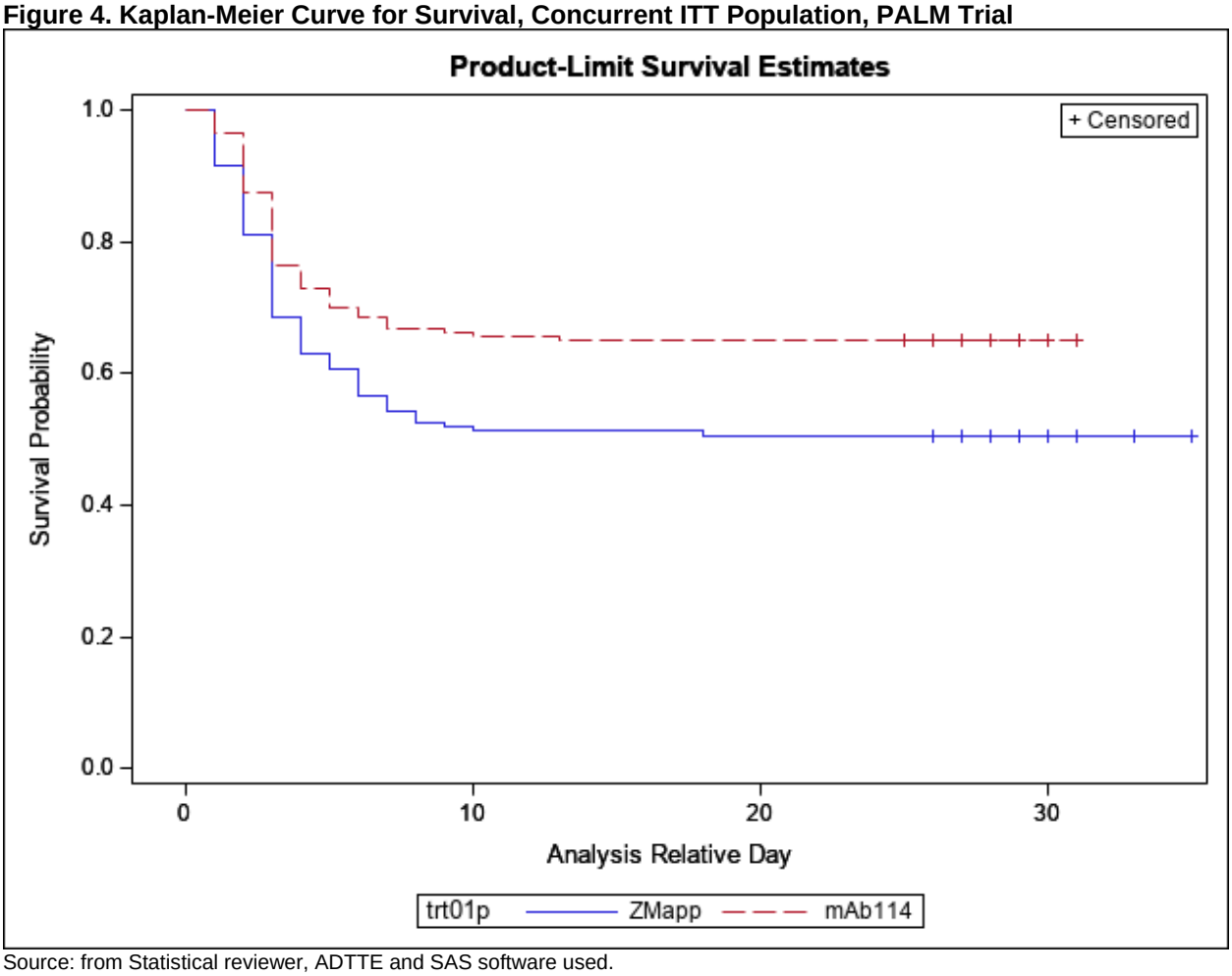
Study Day of Death or Discharge, n (%)	Ansuvimab-zykl (N=174)		ZMapp (N=168)	
	Death	Discharge From ETU	Death	Discharge From ETU
Total number of patients	62	113	84	85
Day 1	6 (3.4)	1 (0.6)	14 (8.3)	0
Day 2	16 (9.2)	0	18 (10.7)	0
Day 3	19 (10.9)	1 (0.6)	21 (12.5)	0
Day 4	6 (3.4)	2 (1.1)	9 (5.4)	0
Day 5	5 (2.9)	3 (1.7)	4 (2.4)	1 (0.6)
Day 6	3 (1.7)	2 (1.1)	7 (4.2)	1 (0.6)
Day 7	3 (1.7)	3 (1.7)	4 (2.4)	1 (0.6)
Day 8	0	2 (1.1)	3 (1.8)	2 (1.2)
Day 9	1 (0.6)	3 (1.7)	1 (0.6)	1 (0.6)
Day 10	1 (0.6)	3 (1.7)	1 (0.6)	5 (3.0)
Day 11	0	4 (2.3)	0	1 (0.6)
Day 12	0	6 (3.4)	0	2 (1.2)
Day 13	1 (0.6)	3 (1.7)	0	2 (1.2)
Day 14	0	7 (4.0)	0	3 (1.8)
Day 15	0	8 (4.6)	0	9 (5.4)
Day 16	0	12 (6.9)	0	8 (4.8)
Day 17	0	5 (2.9)	0	14 (8.3)
Day 18	0	8 (4.6)	1 (0.6)	8 (4.8)
Day 19	0	4 (2.3)	0	2 (1.2)
Day 20	0	9 (5.2)	0	4 (2.4)
Day 21	0	3 (1.7)	0	2 (1.2)
Day 22	0	3 (1.7)	0	3 (1.8)
Day 23	0	2 (1.1)	0	1 (0.6)
Day 24	0	3 (1.7)	0	3 (1.8)
Day 25	0	2 (1.1)	0	2 (1.2)
Day 26	0	2 (1.1)	0	0
Day 27	0	0	0	2 (1.2)
Day 28	0	4 (2.3)	0	0
Day 29–31	0	2 (1.1)	0	1 (0.6)
Day 32–35	0	6 (3.4)	0	4 (2.4)
Day >35	1 (0.6)	1 (0.6)	0	3 (1.8)

Source: Statistical reviewer, ADSL and SAS software were used.
Note: if a subject was discharged on or before their Day 28 visit but died on a subsequent day, that subject may have been included in more than one column.
Abbreviations: ETU, Ebola treatment unit; ITT, intent-to-treat; N, number of subjects; n, number of subjects in subgroup; PALM, PAmoja TuLinde Maisha

KM Curve for the Probability of Survival

The KM curve for the probability of survival is shown in Figure 4. Because most deaths occurred within the first 4 days, the survival probability dropped sharply; thereafter, the survival probability in the ansuvimab-zykl arm remained higher than in the ZMapp arm. A log-rank test indicated a significant difference in the curve over time (p=0.0072).

Figure 4. Kaplan-Meier Curve for Survival, Concurrent ITT Population, PALM Trial



Source: from Statistical reviewer, ADTTE and SAS software used.
Abbreviations: ITT, intent-to-treat; PALM, PAmoja TuLinde Maisha

16.4. Additional Subgroup Analyses for the Primary Efficacy Endpoint

This section supplements the analyses and interpretation presented in Section 6.2.4.3 Of note, the sample sizes for many subgroups were small, which limits the ability to detect trends with certainty. Numerous subgroup analyses were conducted without any adjustment for the multiple analyses, which could result in spurious findings due to chance.

The treatment effect of ansuvimab-zykl compared to ZMapp appeared consistent across most baseline subgroups of age, gender, site, and other baseline factors analyzed, although there were differences in the 28-day mortality rates (Table 52). For example, the 28-day mortality rate for female subjects (58.6%) in the ZMapp arm was higher than that for male subjects (39.5%) in the ZMapp arm, while female (31.6%) and male (39.5%) subjects had similar mortality rates in the ansuvimab-zykl arm. A Forest plot with the same information is presented in Figure 5.

The impact of baseline viral load on the primary efficacy endpoint was discussed in Section 6.3.2. For ALT, AST, and creatinine, the higher the baseline values over the upper limit of normal, the higher the 28-day mortality rate observed in both arms. Subjects who were treated within 5 days from symptom onset to randomization had lower 28-day mortality rates in both

arms than those treated more than 5 days from symptom onset to randomization. In addition, the 28-day mortality rates in the ansuvimab-zykl arm were lower than those in the ZMapp arm across these subgroups.

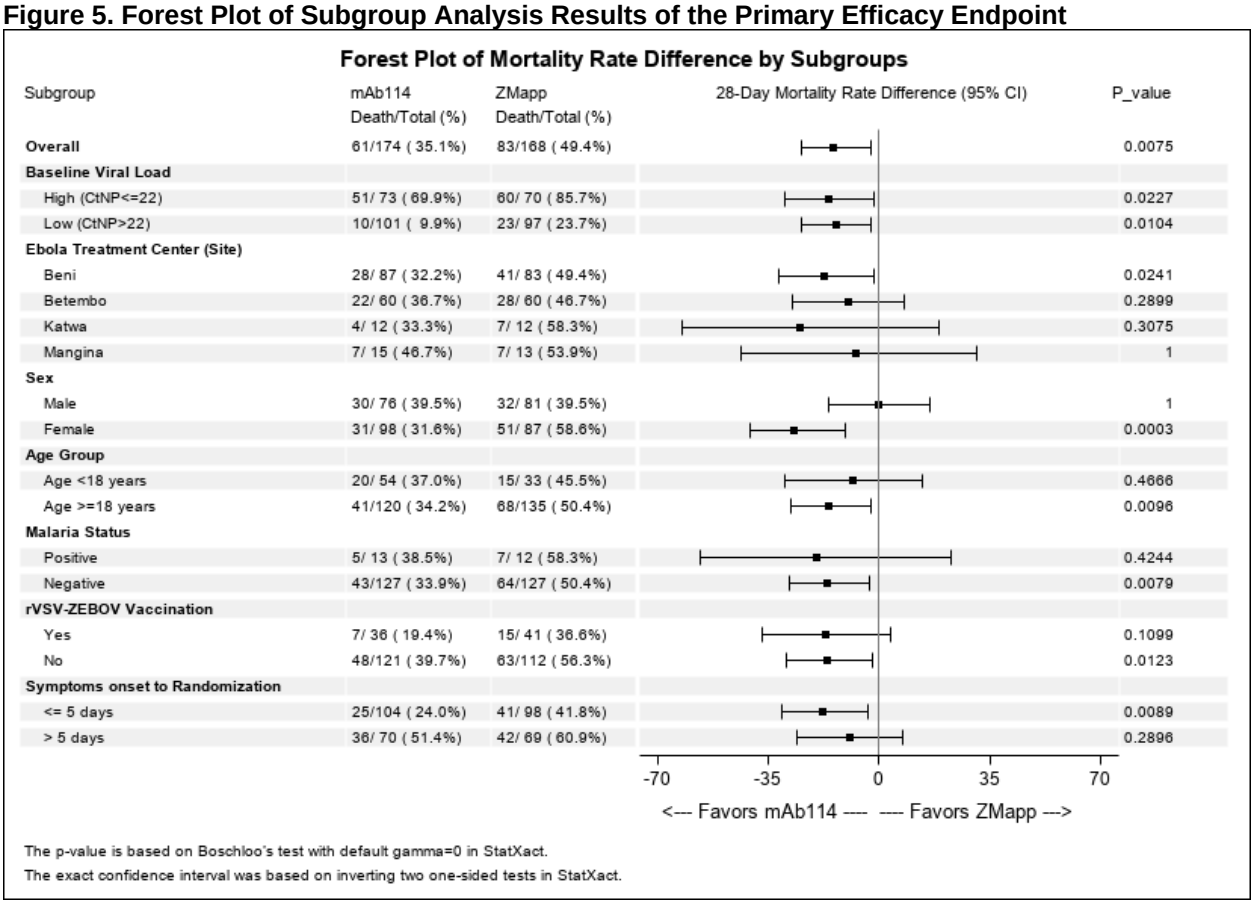
Table 52. Summary of 28-Day Mortality by Selected Baseline Factors, Concurrent ITT Population, PALM Trial

Population/Subpopulation	Ansuvimab-zykl (N=174) Death/Total (%)	ZMapp (N=168) Death/Total (%)	Rate Difference % (95% CI)[a]	Boschloo's 2-Sided P-Value[b]
Concurrent ITT	61/174 (35.1%)	83/168 (49.4%)	-14.4 (-24.8, -2.4)	0.0075
CtNP at BL				
CtNP ≤22	51/73 (69.9%)	60/70 (85.7%)	-15.9 (-29.7, -1.7)	0.0227
CtNP >22	10/101 (9.9%)	23/97 (23.7%)	-13.8 (-24.5, -2.6)	0.0104
Site or ETU				
Beni	28/87 (32.2%)	41/83 (49.4%)	-17.2 (-31.7, -1.7)	0.0241
Betembo	22/60 (36.7%)	28/60 (46.7%)	-10.0 (-27.5, 8.0)	0.2899
Katwa	4/12 (33.3%)	7/12 (58.3%)	-25.0 (-62.4, 18.8)	0.3075
Mangina	7/15 (46.7%)	7/13 (53.9%)	-7.2 (-43.6, 30.7)	1.0000
Sex				
Female	31/98 (31.6%)	51/87 (58.6%)	-27.0 (-40.7, -10.9)	0.0003
Male	30/76 (39.5%)	32/81 (39.5%)	0.0 (-15.8, 15.8)	1.0
Age group				
≤5 years	11/26 (42.3%)	8/19 (42.1%)	0.2 (-29.4, 29.1)	1.0
6–12 years	5/15 (33.3%)	3/7 (42.9%)	-9.5 (-53.7, 32.9)	1.0
13–17 years	4/13 (30.8%)	4/7 (57.1%)	-26.4 (-66.5, 20.4)	0.2994
18–49 years	32/93 (34.4%)	57/114 (50.0%)	-15.6 (-28.9, -1.2)	0.0297
50–64 years	6/21 (28.6%)	8/18 (44.4%)	-15.9 (-45.3, 16.7)	0.2889
≥65 years	3/6 (50.0%)	3/3 (100%)	-50.0 (-90.2, 28.3)	0.2578
Age group				
<18 years	20/54 (37.0%)	15/33 (45.5%)	-8.4 (-29.8, 13.6)	0.4666
≥18 years	41/120 (34.2%)	68/135 (50.4%)	-16.2 (-28.1, -2.8)	0.0096
Malaria status				
Positive	5/13 (38.5%)	7/12 (58.3%)	-19.9 (-56.4, 22.9)	0.4244
Negative	43/127 (33.9%)	64/127 (50.4%)	-16.5 (-28.4, -3.1)	0.0079
Unknown	13/34 (38.2%)	12/29 (41.4%)	-3.1 (-28.4, 21.5)	1.0
rVSV-ZEBOV vaccination at BL				
Yes	7/36 (19.4%)	15/41 (36.6%)	-17.1 (-36.9, 3.7)	0.1099
No	48/121 (39.7%)	63/112 (56.3%)	-16.6 (-29.3, -2.3)	0.0123
Unknown	6/17 (35.3%)	5/15 (33.3%)	2.0 (-32.0, 35.7)	1.0
Reported days before ETU admission for subjects with rVSV-ZEBOV vaccination at BL				
<10 days	5/24 (20.8%)	9/23 (39.1%)	-18.3 (-43.8, 8.8)	0.1729
≥10 days	2/12 (16.7%)	6/18 (33.3%)	-16.7 (-46.9, 19.1)	0.3516
Not vaccinated				
Days from symptom onset to randomization (median=5 days)				
≤5 days	25/104 (24.0%)	41/98 (41.8%)	-17.8 (-30.7, -3.4)	0.0089
>5 days	36/70 (51.4%)	42/69 (60.9%)	-9.4 (-25.9, 7.3)	0.2896
Days from symptom onset to randomization by quartile				
<Q1 (3.0 days)	6/36 (16.7%)	10/28 (35.7%)	-19.1 (-41.3, 3.5)	0.0777
Q1, ≤Q2 (5.0)	19/68 (27.9%)	31/70 (44.3%)	-16.3 (-32.1, 0.3)	0.0444
Q2, ≤Q3 (7.0)	14/28 (50.0%)	22/32 (68.8%)	-18.8 (-42.6, 7.2)	0.1621
>Q3 (7.0 days)	22/42 (52.4%)	20/37 (54.1%)	-1.7 (-23.7, 20.5)	1.0

Population/Subpopulation	Ansuvimab-zykl (N=174) Death/Total (%)	ZMapp (N=168) Death/Total (%)	Rate Difference % (95% CI)[a]	Boschloo's 2-Sided P-Value[b]
Baseline ALT (U/L)				
≤5xULN	10/83 (12.1%)	13/65 (20.0%)	-8.0 (-20.9, 4.2)	0.2425
>5xULN	35/58 (60.3%)	52/65 (80.0%)	-19.7 (-35.5, -2.9)	0.0148
Baseline ALT (U/L)				
≤10xULN	16/101 (15.8%)	28/89 (31.5%)	-15.6 (-28.1, -2.7)	0.0130
>10xULN	29/40 (72.5%)	37/41 (90.2%)	-17.7 (-35.7, -0.4)	0.0448
Baseline AST (U/L)				
≤5xULN	1/48 (2.1%)	7/34 (20.6%)	-18.5 (-35.6, -4.1)	0.0064
>5xULN	11/51 (21.6%)	24/55 (43.6%)	-22.1 (-39.2, -3.1)	0.0195
Baseline AST (U/L)				
≤10xULN	1/57 (1.8%)	8/46 (17.4%)	-15.6 (-29.7, -4.2)	0.0080
>10xULN	11/42 (26.2%)	23/43 (53.5%)	-27.3 (-46.8, -5.5)	0.0115
Baseline creatinine (mg/dL)				
≤1xULN (1.2)	17/97 (17.5%)	18/65 (27.7%)	-10.2 (-24.2, 3.4)	0.1481
>1xULN	27/46 (58.7%)	45/62 (72.6%)	-13.9 (-32.0, 4.5)	0.1283
Baseline creatinine (mg/dL)				
≤3 mg/dL	23/111 (20.7%)	33/90 (36.7%)	-16.0 (-28.8, -2.2)	0.0158
>3 mg/dL	21/32 (65.6%)	30/37 (81.1%)	-15.5 (-36.8, 6.0)	0.1478

Source: Statistical reviewer; ADSL and SAS software were used.
[a] The exact confidence interval was based on inverting two one-sided tests in StatXact.
[b] P-value is based on Boschloo's test with default gamma =0 in StatXact.
Abbreviations: ALT, alanine aminotransferase; BL, baseline; CI, confidence interval; CtNP, cycle-threshold nucleoprotein gene targets; ETU, Ebola treatment unit; ITT, intent-to-treat; N, number of subjects; PALM, PAmoja TuLinde Maisha; rVSV, recombinant vesicular stomatitis virus; ULN, upper limit of normal

Figure 5. Forest Plot of Subgroup Analysis Results of the Primary Efficacy Endpoint



Source: Statistical reviewer, ADSL and SAS software were used.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CtNP, cycle-threshold nucleoprotein gene targets; rVSV, recombinant vesicular stomatitis virus; ULN, upper limit of normal

Table 53 was generated (b) (4) because the age cutoff values were different from my previous age subgroup analyses.

Table 53. 28-Day Mortality Rates by Age Groups, Concurrent ITT, PALM Trial

Mortality Rate by Age Group	Ansuvimab-zykl (N=174) Death/Total (%)	ZMapp (N=168) Death/Total (%)
Overall	61/174 (35.1%)	83/168 (49.4%)
<18 years	20/54 (37.0%)	15/33 (45.5%)
Adults (≥18 years)	41/120 (34.2%)	68/135 (50.4%)
For subjects ≥18 years of age		
≥18–<50 years of age	32/93 (34.4%)	57/114 (50.0%)
≥50–<65 years of age	6/21 (28.6%)	8/18 (44.4%)
≥65 years of age	3/6 (50.0%)	3/3 (100%)
For subjects <18 years of age		
≥12–<18 years of age	5/15 (33.3%)	5/9 (55.6%)
≥6–<12 years of age	4/13 (30.8)	2/5 (40.0%)
<6 years of age	11/26 (42.3%)	8/19 (42.1%)
For subjects <6 years of age		
≥1–<6 years of age	8/15 (53.3%)	7/12 (58.3%)
≥1 month–<1 year	3/10 (30.0%)	1/5 (20.0%)
<1 month	0/1	0/2

Source: Statistical reviewer; ADSL and SAS software used.
Abbreviations: ITT, intent-to-treat; N, number of subjects; PALM, PAmoja TuLinde Maisha

16.5. Logistic Regression of the Primary Efficacy Endpoint by Treatment and Baseline Factors

A logistic regression analysis was used to assess the impact of baseline factors on 28-day mortality. FDA included the same covariates in the model as the Applicant:

- Treatment
- Baseline CtNP category (categorical: <=22, >22)
- Sex (categorical: Male, Female)
- Age (continuous)
- Baseline Ebola vaccination status (categorical: Y, N, Unknown)
- Ebola Treatment Unit (ETU, site)

FDA analysis resulted in similar results as reported in the clinical study report (i.e., the logistic regression indicated that in addition to treatment, 28-day mortality rate was influenced by baseline CtNP level) (Table 54). No other covariates significantly impacted mortality rate.

Table 54. Summary of Logistic Regression at 28-Day Mortality Adjusted by Covariates (the Applicant's Approach), Concurrent ITT Population, PALM Trial

Dependent Variables	Odds Ratio Estimation	95% Wald CI	P-Value of Wald Chi-Square
Treatment			
ZMapp vs. ansuvimab-zykl	2.91	(1.61, 5.26)	0.0004
Ebovacfl			
No vs. Yes	2.03	(0.99, 4.15)	0.1116
Unknown vs. Yes	1.16	(0.36, 3.80)	
CtNPGr1			
≤22 vs. >22	21.88	(11.85, 40.39)	<0.0001
Age	1.01	(1.00, 1.03)	0.0884
Sex			
Male vs. female	0.73	(0.42, 1.29)	0.2808
Site			
Beni vs. Mangina	0.72	(0.25, 2.04)	0.8626
Butembo vs. Mangina	0.85	(0.30, 2.42)	
Katwa vs. Mangina	1.07	(0.26, 4.46)	

Source: Statistical reviewer; ADSL and SAS software used.
Abbreviations: CI, confidence interval; CtNPGr1, baseline CtNP category; Ebovacfl, baseline Ebola vaccination status

We conducted another logistic regression by including one more baseline covariate,

- Days from symptom onset to randomization (continuous)

We used stepwise model selection with entry criteria =0.3 and stay criteria =0.35 to selecting the final logistic regression model. The final regression model only included treatment, baseline CtNP category, days from symptom onset to randomization, baseline Ebola vaccination status, and age. Results indicated that 28-day mortality rate was influenced by baseline CtNP level and was slightly impacted by the days from symptom onset to randomization (Table 55). These results are consistent with the subgroup analysis results in Section 16.4.

Table 55. Summary of Logistic Regression at 28-Day Mortality Adjusted by the Model Selection of Potential Covariates, Concurrent ITT Population, PALM Trial

Dependent Variables	Odds Ratio Estimation	95% Wald CI	P-Value of Wald Chi-Square
Treatment			
ZMapp vs. ansuvimab-zykl	2.87	(1.59, 5.18)	0.0005
Ebovacfl			
No vs. Yes	1.63	(0.78, 3.38)	0.2022
Unknown vs. Yes	0.80	(0.25, 2.52)	
CtNPGr1			
≤22 vs. >22	21.61	(11.71, 39.87)	<0.0001
Age	1.02	(1.00, 1.03)	0.0777
Symondys	1.09	(1.00, 1.18)	0.0327

Source: Statistical reviewer; ADSL and SAS software used.
Abbreviations: CI, confidence interval; CtNPGr1, baseline CtNP category; Ebovacfl, baseline Ebola vaccination status; Symondys, days from symptom onset to randomization

The results of sub-subgroup analysis between baseline viral load and days from symptom onset to randomization are listed in the Table 56. The baseline viral load had dominant impact on the 28-day mortality rate, and days from symptom onset to randomization had some additional impact as well for both arms. The lower baseline viral load, the earlier receiving treatment, the lower the mortality rate.

Table 56. Sub-Subgroup Analyses of Viral load at Baseline and the Number of Days From Symptoms Onset to Randomization on the Primary Efficacy Endpoint (28-Day Mortality), Concurrent ITT, PALM Trial

Population / Subpopulation	Ansuvimab-zykl (N=174) Death/Total (%)	ZMapp (N=168) Death/Total (%)	Rate Difference % (95% CI)[a]	Boschloo's 2-Sided P-Value[b]
Concurrent ITT	61/174 (35.1%)	83/168 (49.4%)	-14.4 (-24.8, -2.4)	0.0075
Viral load cross the number of days from symptoms onset to randomization				
CtNP ≤22, onset ≤5 days	24/39 (61.5%)	27/35 (77.1%)	-15.6 (-36.3, 6.1)	0.1712
CtNP ≤22, onset >5 days	27/34 (79.4%)	33/35 (94.3%)	-14.9 (-32.8, 1.7)	0.0672
CtNP >22, onset ≤5 days	1/65 (1.5%)	14/63 (22.2%)	-20.7 (-33.0, -9.0)	0.0002
CtNP >22, onset >5 days	9/36 (25.0%)	9/34 (26.5%)	-1.5 (-22.6, 19.5)	1.0

Source: Statistical reviewer; ADSL and SAS software used.
[a] The exact confidence interval was based on inverting two one-sided tests in StatXact.
[b] P-value is based on Boschloo's test with a default gamma of 0 in StatXact.
Abbreviations: CI, confidence interval; CtNP, cycle-threshold nucleoprotein gene targets; ITT, intent-to-treat; PALM, PAmoja TuLinde Maisha

16.6. Twenty-Eight-Day Mortality Rates of ZMapp in PREVAIL II and PALM Trials

The overall 28-day mortality rate of ZMapp in the current PALM Trial was 49.4% (83/168) with Clopper-Pearson exact 95% CI (41.6%, 57.2%), while the 28-day mortality rate in the PREVAIL II trial was 22.2% (8/36) with a Clopper-Pearson exact 95% CI (10.1%, 39.2%). Examination of the proportions of baseline viral load categories, which are almost identical (Tables 57 and 58), shows that the difference in mortality rates between the PREVAIL II and PALM Trials was due to factors other than baseline viral load. The 28-day mortality rates of the low and high baseline

viral load groups were higher for ZMapp than in the PALM Trial compared to the PREVAIL II Trial.

The study protocol stated that "a mortality rate of 30% in the ZMapp + oSOC control arm was based, in part, on a meta-analysis of eight clinical studies conducted during the 2014 to 2016 West African Ebola outbreak. This analysis indicated that mortality rates within PREVAIL II were lower than other studies across both treatment and control arms. Hence, the expected mortality rate with ZMapp in this trial may be higher than the point estimate from PREVAIL II." The 28-day mortality rate in the PALM Trial seems to have verified this statement.

Table 57. Subgroup Analysis of Primary Endpoint by Baseline Viral Load in the PREVAIL II Trial

CtNP Subgroup	Proportion (N=71)		28-Day Mortality Rate	
	ZMapp (n=36)	oSOC (n=35)	ZMapp	oSOC
CtNP ≤22	15 (42%)	15 (43%)	7/15 (46.7%)	9/15 (60%)
CtNP >22	21 (58%)	20 (57%)	1/21 (4.8%)	4/20 (20%)

Source: Dr. Daniel Rubin's Statistical Review for IND 125530/SN0043 on July 15, 2016 for PREVAIL II Trial
Abbreviations: CtNP, cycle-threshold nucleoprotein gene targets; N, number of subjects; n, number of subjects in subgroup; oSOC, optimized standard of care

Table 58. Subgroup Analysis of Primary Endpoint by Baseline Viral Load in the PALM Trial

	Proportion (N=342)		28-Day Mortality Rate	
	ZMapp (n=168)[1]	Ansuvimab-zykl (n=174)	ZMapp	Ansuvimab-zykl
CtNP ≤22	70 (42%)	73 (42%)	60/70 (85.7%)	51/73 (69.9%)
CtNP >22	97 (58%)	101 (58%)	23/97 (23.7%)	10/101 (9.9%)

Source: Statistical reviewer, ADSL and SAS software were used.
[1] One subject did not have a Ct value because he/she was 1 day of age.
Abbreviations: CtNP, cycle-threshold nucleoprotein gene targets; N, number of subjects; n, number of subjects in subgroup; PALM, PAmoja TuLinde Maisha

17. Clinical Safety: Additional Information and Assessment

The following table (Table 59) provides a detailed listing of AEs by system organ class and preferred term. The data were also presented in a summarized form in Section 7 (Table 27) and (b) (4) Inclusion of signs and symptoms from death reports did not significantly affect the overall profile for the most common adverse reactions; (b) (4)

Table 59. Adverse Events by System Organ Class and Preferred Term, Safety Population, PALM Trial

System Organ Class Preferred Term	Ansuvimab-zykl N=173 n (%)	ZMapp N=168 n (%)	Risk Difference (95% CI)[1]
Infections and infestations (SOC)	1 (0.6)	0	0.6 (-0.5, 1.7)
Cerebral malaria	1 (0.6)	0	0.6 (-0.5, 1.7)
Eye disorders (SOC)	1 (0.6)	1 (0.6)	0.0 (-1.6, 1.6)
Blindness unilateral	1 (0.6)	0	0.6 (-0.5, 1.7)
Eye pain	0	1 (0.6)	-0.6 (-1.8, 0.6)

System Organ Class Preferred Term	Ansuvimab-zykl N=173 n (%)	ZMapp N=168 n (%)	Risk Difference (95% CI)[1]
Pregnancy, puerperium and perinatal conditions (SOC)	1 (0.6)	2 (1.2)	-0.6 (-2.6, 1.4)
Fetal death	1 (0.6)	1 (0.6)	0.0 (-1.6, 1.6)
Umbilical cord short	0	1 (0.6)	-0.6 (-1.8, 0.6)
Immune system disorders (SOC)	0	1 (0.6)	-0.6 (-1.8, 0.6)
Anaphylactic shock	0	1 (0.6)	-0.6 (-1.8, 0.6)
Injury, poisoning and procedural complications (SOC)	0	1 (0.6)	-0.6 (-1.8, 0.6)
Urethral injury	0	1 (0.6)	-0.6 (-1.8, 0.6)
Musculoskeletal and connective tissue disorders (SOC)	0	1 (0.6)	-0.6 (-1.8, 0.6)
Back pain	0	1 (0.6)	-0.6 (-1.8, 0.6)
Metabolism and nutrition disorders (SOC)	4 (2.3)	6 (3.6)	-1.3 (-4.9, 2.3)
Malnutrition	1 (0.6)	0	0.6 (-0.5, 1.7)
Decreased appetite	3 (1.7)	6 (3.6)	-1.9 (-5.3, 1.5)
Skin and subcutaneous tissue disorders (SOC)	2 (1.2)	5 (3.0)	-1.8 (-4.8, 1.2)
Decubitus ulcer	1 (0.6)	0	0.6 (-0.5, 1.7)
Stevens-Johnson syndrome	1 (0.6)	0	0.6 (-0.5, 1.7)
Pruritus	0	2 (1.2)	-1.2 (-2.8, 0.4)
Rash	0	3 (1.8)	-1.8 (-3.8, 0.2)
Psychiatric disorders (SOC)	4 (2.3)	8 (4.8)	-2.5 (-6.4, 1.4)
Behaviour disorder	2 (1.2)	0	1.2 (-0.4, 2.8)
Psychotic disorder	1 (0.6)	0	0.6 (-0.5, 1.7)
Agitation	1 (0.6)	8 (4.8)	-4.2 (-7.6, -0.8)
Nervous system disorders (SOC)	7 (4.0)	18 (10.7)	-6.7 (-12.2, -1.2)
Hydrocephalus	0	1 (0.6)	-0.6 (-1.8, 0.6)
Dizziness	3 (1.7)	5 (3.0)	-1.3 (-4.5, 1.9)
Seizure	1 (0.6)	6 (3.6)	-3.0 (-6.0, 0.0)
Headache	3 (1.7)	8 (4.8)	-3.1 (-6.9, 0.7)
Investigations (SOC)	6 (3.5)	19 (11.3)	-7.8 (-13.3, -2.3)
Oxygen saturation decreased	6 (3.5)	19 (11.3)	-7.8 (-13.3, -2.3)
Gastrointestinal disorders (SOC)	25 (14.5)	59 (35.1)	-20.6 (-29.5, -11.7)
Dyspepsia	1 (0.6)	1 (0.6)	0.0 (-1.6, 1.6)
Haematemesis	1 (0.6)	1 (0.6)	0.0 (-1.6, 1.6)
Abdominal distension	0	1 (0.6)	-0.6 (-1.8, 0.6)
Dysphagia	0	1 (0.6)	-0.6 (-1.8, 0.6)
Melaena	0	1 (0.6)	-0.6 (-1.8, 0.6)
Abdominal pain upper	1 (0.6)	3 (1.8)	-1.2 (-3.5, 1.1)
Abdominal pain	0	5 (3.0)	-3.0 (-5.6, -0.4)
Nausea	6 (3.5)	12 (7.1)	-3.6 (-8.4, 1.2)
Diarrhoea	15 (8.7)	31 (18.5)	-9.8 (-17.0, -2.6)
Vomiting	14 (8.1)	38 (22.6)	-14.5 (-22.0, -7.0)
Cardiac disorders (SOC)	15 (8.7)	58 (34.5)	-25.8 (-34.1, -17.5)
Palpitations	0	1 (0.6)	-0.6 (-1.8, 0.6)
Bradycardia	0	5 (3.0)	-3.0 (-5.6, -0.4)
Tachycardia	15 (8.7)	53 (31.5)	-22.8 (-31.0, -14.6)
Respiratory, thoracic and mediastinal disorders (SOC)	16 (9.2)	60 (35.7)	-26.5 (-34.9, -18.1)
Epistaxis	0	1 (0.6)	-0.6 (-1.8, 0.6)
Nasal flaring	0	1 (0.6)	-0.6 (-1.8, 0.6)
Hiccups	2 (1.2)	4 (2.4)	-1.2 (-4.0, 1.6)
Cough	1 (0.6)	6 (3.6)	-3.0 (-6.0, 0.0)

System Organ Class Preferred Term	Ansuvimab-zykl N=173 n (%)	ZMapp N=168 n (%)	Risk Difference (95% CI)[1]
Dyspnoea	6 (3.5)	12 (7.1)	-3.6 (-8.4, 1.2)
Tachypnoea	10 (5.8)	47 (28.0)	-22.2 (-29.8, -14.6)
Vascular disorders (SOC)	15 (8.7)	66 (39.3)	-30.6 (-39.1, -22.1)
Haemorrhage	1 (0.6)	0	0.6 (-0.5, 1.7)
Flushing	0	1 (0.6)	-0.6 (-1.8, 0.6)
Hypertension	2 (1.2)	17 (10.1)	-8.9 (-13.7, -4.1)
Hypotension	13 (7.5)	52 (31.0)	-23.5 (-31.5, -15.5)
General disorders and administration site conditions (SOC)	35 (20.2)	116 (69.0)	-48.8 (-58.0, -39.6)
Oedema peripheral	1 (0.6)	1 (0.6)	0.0 (-1.6, 1.6)
Hypothermia	1 (0.6)	2 (1.2)	-0.6 (-2.6, 1.4)
Feeling hot	0	1 (0.6)	-0.6 (-1.8, 0.6)
Oedema	0	1 (0.6)	-0.6 (-1.8, 0.6)
Malaise	0	4 (2.4)	-2.4 (-4.7, -0.1)
Chest pain	0	7 (4.2)	-4.2 (-7.2, -1.2)
Chills	8 (4.6)	55 (32.7)	-28.1 (-35.9, -20.3)
Pyrexia	30 (17.3)	97 (57.7)	-40.4 (-49.8, -31.0)

Source: Analysis by Clinical Data Scientist of adae.xpt; Software: Python
Treatment-emergent adverse events defined as Any AE occurred after first treatment
[1] Risk difference column shows absolute difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

Serious Adverse Events

Table 60 lists SAEs by system organ class and preferred term occurring in the ansuvimab-zykl and ZMapp arms, and was presented in a summarized form in Section 7 (Table 29). There were a total of 11 SAEs in the ansuvimab-zykl arm, none of which led to drug discontinuation and none were determined to be related to the study drug.

Table 60. Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, PALM Trial

System Organ Class Preferred Term	Ansuvimab-zykl N=173 n (%)	ZMapp N=168 n (%)	Risk Difference (95% CI)[1]
Psychiatric disorders (SOC)	3 (1.7)	0	1.7 (-0.2, 3.6)
Behaviour disorder	2 (1.2)	0	1.2 (-0.4, 2.8)
Psychotic disorder	1 (0.6)	0	0.6 (-0.5, 1.7)
Skin and subcutaneous tissue disorders (SOC)	2 (1.2)	0	1.2 (-0.4, 2.8)
Decubitus ulcer	1 (0.6)	0	0.6 (-0.5, 1.7)
Stevens-Johnson syndrome	1 (0.6)	0	0.6 (-0.5, 1.7)
Eye disorders (SOC)	1 (0.6)	0	0.6 (-0.5, 1.7)
Blindness unilateral	1 (0.6)	0	0.6 (-0.5, 1.7)
Infections and infestations (SOC)	1 (0.6)	0	0.6 (-0.5, 1.7)
Cerebral malaria	1 (0.6)	0	0.6 (-0.5, 1.7)
Metabolism and nutrition disorders (SOC)	1 (0.6)	0	0.6 (-0.5, 1.7)
Malnutrition	1 (0.6)	0	0.6 (-0.5, 1.7)
Gastrointestinal disorders (SOC)	1 (0.6)	1 (0.6)	0.0 (-1.6, 1.6)
Dyspepsia	1 (0.6)	0	0.6 (-0.5, 1.7)
Diarrhoea	0	1 (0.6)	-0.6 (-1.8, 0.6)
Vomiting	0	1 (0.6)	-0.6 (-1.8, 0.6)

System Organ Class Preferred Term	Ansuvimab-zykl N=173 n (%)	ZMapp N=168 n (%)	Risk Difference (95% CI)[1]
General disorders and administration site conditions (SOC)	1 (0.6)	1 (0.6)	0.0 (-1.6, 1.6)
Oedema peripheral	1 (0.6)	1 (0.6)	0.0 (-1.6, 1.6)
Pregnancy, puerperium and perinatal conditions (SOC)	1 (0.6)	2 (1.2)	-0.6 (-2.6, 1.4)
Fetal death	1 (0.6)	1 (0.6)	0.0 (-1.6, 1.6)
Umbilical cord short	0	1 (0.6)	-0.6 (-1.8, 0.6)
Immune system disorders (SOC)	0	1 (0.6)	-0.6 (-1.8, 0.6)
Anaphylactic shock	0	1 (0.6)	-0.6 (-1.8, 0.6)
Injury, poisoning and procedural complications (SOC)	0	1 (0.6)	-0.6 (-1.8, 0.6)
Urethral injury	0	1 (0.6)	-0.6 (-1.8, 0.6)
Nervous system disorders (SOC)	0	1 (0.6)	-0.6 (-1.8, 0.6)
Hydrocephalus	0	1 (0.6)	-0.6 (-1.8, 0.6)

Source: Analysis by Clinical Data Scientist of adae.xpt; Software: Python
Treatment-emergent adverse events defined as Any AE occurred after first treatment
[1] Risk difference column shows absolute difference (with 95% confidence interval) between total treatment and comparator.
An SAE is an AE that results in one or more of the following outcomes: death, a life-threatening event (places the participant at immediate risk of death from the event as it occurred), an inpatient hospitalization or prolongation of an existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions a congenital anomaly/birth defect or fetal loss/miscarriage, or a medically important event.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

Adverse Events That Led to Drug Discontinuations

Table 61 lists AEs that led to study drug discontinuation, by system organ class and preferred term in the ansuvimab-zykl and ZMapp arms. As described in Section 7.6.4 two subjects (1.1%) in the ansuvimab-zykl arm of the PALM RCT did not receive their complete infusion because of AEs that occurred during infusion. In both subjects, the drug was discontinued, and the subjects received intravenous fluids and supportive care. Both subjects subsequently died (Subject (b) (6) on Day 2 and Subject (b) (6) on Day 8).

Table 61. Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Safety Population, PALM Trial

System Organ Class Preferred Term	Ansuvimab-zykl N=173 n (%)	ZMapp N=168 n (%)	Risk Difference (95% CI)[1]
Metabolism and nutrition disorders (SOC)	0	1 (0.6)	-0.6 (-1.8, 0.6)
Decreased appetite	0	1 (0.6)	-0.6 (-1.8, 0.6)
Psychiatric disorders (SOC)	0	1 (0.6)	-0.6 (-1.8, 0.6)
Agitation	0	1 (0.6)	-0.6 (-1.8, 0.6)
Nervous system disorders (SOC)	0	2 (1.2)	-1.2 (-2.8, 0.4)
Headache	0	1 (0.6)	-0.6 (-1.8, 0.6)
Seizure	0	1 (0.6)	-0.6 (-1.8, 0.6)
Investigations (SOC)	0	3 (1.8)	-1.8 (-3.8, 0.2)
Oxygen saturation decreased	0	3 (1.8)	-1.8 (-3.8, 0.2)
Respiratory, thoracic and mediastinal disorders (SOC)	2 (1.2)	6 (3.6)	-2.4 (-5.6, 0.8)
Dyspnoea	1 (0.6)	1 (0.6)	0.0 (-1.6, 1.6)
Cough	0	1 (0.6)	-0.6 (-1.8, 0.6)
Tachypnoea	2 (1.2)	5 (3.0)	-1.8 (-4.8, 1.2)
Gastrointestinal disorders (SOC)	0	4 (2.4)	-2.4 (-4.7, -0.1)
Diarrhoea	0	1 (0.6)	-0.6 (-1.8, 0.6)
Dyspepsia	0	1 (0.6)	-0.6 (-1.8, 0.6)
Vomiting	0	3 (1.8)	-1.8 (-3.8, 0.2)

System Organ Class Preferred Term	Ansuvimab-zykl N=173 n (%)	ZMapp N=168 n (%)	Risk Difference (95% CI)[1]
General disorders and administration site conditions (SOC)	1 (0.6)	8 (4.8)	-4.2 (-7.6, -0.8)
Chest pain	0	1 (0.6)	-0.6 (-1.8, 0.6)
Chills	1 (0.6)	4 (2.4)	-1.8 (-4.4, 0.8)
Pyrexia	1 (0.6)	7 (4.2)	-3.6 (-6.8, -0.4)
Cardiac disorders (SOC)	0	7 (4.2)	-4.2 (-7.2, -1.2)
Tachycardia	0	7 (4.2)	-4.2 (-7.2, -1.2)
Vascular disorders (SOC)	1 (0.6)	10 (6.0)	-5.4 (-9.2, -1.6)
Hypertension	0	2 (1.2)	-1.2 (-2.8, 0.4)
Hypotension	1 (0.6)	8 (4.8)	-4.2 (-7.6, -0.8)

Source: Analysis by Clinical Data Scientist of adae.xpt; Software: Python
Treatment-emergent adverse events defined as Any AE occurred after first treatment
[1] Risk difference column shows absolute difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

Deaths

Table 62 lists the deaths that occurred in the ansuvimab-zykl and ZMapp arms. Deaths are discussed in Section 6.2.4 as a primary efficacy endpoint. One SAE in the ansuvimab-zykl arm that led to death is discussed in Section 7.6.2. Subject (b) (6) was a female newborn to an EBOV mother who was treated the day after birth and subsequently developed malnutrition that resulted in death 45 days after complete recovery from the EBOV infection.

Table 62. List of Deaths, Safety Population, PALM Trial

Study Arm	Subject ID	Age	Sex	Cause of Death	Study Day of Death	Duration of Exposure (Days)
Ansuvimab-zykl	19-I-0003 (b) (6)	30	F	Evd	2	1
Ansuvimab-zykl	19-I-0003	8	F	Evd	9	1
Ansuvimab-zykl	19-I-0003	22	F	Evd	6	1
Ansuvimab-zykl	19-I-0003	6	F	Evd	2	1
Ansuvimab-zykl	19-I-0003	85	F	Evd	1	1
Ansuvimab-zykl	19-I-0003	7	M	Evd	3	1
Ansuvimab-zykl	19-I-0003	2	M	Evd	4	1
Ansuvimab-zykl	19-I-0003	45	F	Evd	3	1
Ansuvimab-zykl	19-I-0003	50	M	Evd	5	1
Ansuvimab-zykl	19-I-0003	28	M	Evd	4	1
Ansuvimab-zykl	19-I-0003	9	F	Evd	6	1
Ansuvimab-zykl	19-I-0003	13	F	Evd	2	1
Ansuvimab-zykl	19-I-0003	26	M	Evd	2	1
Ansuvimab-zykl	19-I-0003	27	F	Evd	2	1
Ansuvimab-zykl	19-I-0003	18	F	Evd	3	1
Ansuvimab-zykl	19-I-0003	19	F	Evd	3	1
Ansuvimab-zykl	19-I-0003	42	M	Evd	3	1
Ansuvimab-zykl	19-I-0003	40	F	Evd	4	1
Ansuvimab-zykl	19-I-0003	23	F	Evd	3	1
Ansuvimab-zykl	19-I-0003	50	F	Evd	7	1
Ansuvimab-zykl	19-I-0003	54	M	Evd	1	1
Ansuvimab-zykl	19-I-0003	4	M	Evd	3	1
Ansuvimab-zykl	19-I-0003	23	M	Evd	2	1
Ansuvimab-zykl	19-I-0003	17	M	Evd	1	1
Ansuvimab-zykl	19-I-0003	12	M	Evd	13	1

Study Arm	Subject ID	(b) (6)	Age	Sex	Cause of Death	Study Day of Death	Duration of Exposure (Days)
Ansuvimab-zykl	19-I-0003		16	M	Evd	1	1
Ansuvimab-zykl	19-I-0003		3	M	Evd	3	1
Ansuvimab-zykl	19-I-0003		56	F	Evd	3	1
Ansuvimab-zykl	19-I-0003		10	M	Evd	2	1
Ansuvimab-zykl	19-I-0003		42	F	Evd	2	1
Ansuvimab-zykl	19-I-0003		16	F	Evd	3	1
Ansuvimab-zykl	19-I-0003		20	M	Evd	3	1
Ansuvimab-zykl	19-I-0003		24	F	Evd	6	1
Ansuvimab-zykl	19-I-0003		27	M	Evd	4	1
Ansuvimab-zykl	19-I-0003		73	F	Evd	2	1
Ansuvimab-zykl	19-I-0003		68	M	Evd	3	1
Ansuvimab-zykl	19-I-0003		16	M	Evd	5	1
Ansuvimab-zykl	19-I-0003		47	M	Evd	2	1
Ansuvimab-zykl	19-I-0003		3	M	Evd	2	1
Ansuvimab-zykl	19-I-0003		30	F	Evd	4	1
Ansuvimab-zykl	19-I-0003		19	F	Evd	2	1
Ansuvimab-zykl	19-I-0003		22	F	Evd	3	1
Ansuvimab-zykl	19-I-0003		40	M	Evd	3	1
Ansuvimab-zykl	19-I-0003		2	F	Evd	5	1
Ansuvimab-zykl	19-I-0003		29	F	Evd	2	1
Ansuvimab-zykl	19-I-0003		31	M	Evd	4	1
Ansuvimab-zykl	19-I-0003		28	F	Unknown	45	1
Ansuvimab-zykl	19-I-0003		37	M	Evd	7	1
Ansuvimab-zykl	19-I-0003		35	M	Evd	7	1
Ansuvimab-zykl	19-I-0003		20	M	Evd	3	1
Ansuvimab-zykl	19-I-0003		18	M	Evd	2	1
Ansuvimab-zykl	19-I-0003		28	M	Evd	5	1
Ansuvimab-zykl	19-I-0003		23	M	Evd	5	1
Ansuvimab-zykl	19-I-0003		1	M	Evd	3	1
Ansuvimab-zykl	19-I-0003		32	F	Evd	2	1
Ansuvimab-zykl	19-I-0003		38	F	Evd	2	1
Ansuvimab-zykl	19-I-0003		60	F	Evd	3	1
Ansuvimab-zykl	19-I-0003		28	M	Evd	3	1
ZMapp	19-I-0003		34	F	Evd	3	1
ZMapp	19-I-0003		23	M	Evd	4	1
ZMapp	19-I-0003		16	M	Evd	2	1
ZMapp	19-I-0003		34	F	Evd	2	1
ZMapp	19-I-0003		58	F	Evd	3	1
ZMapp	19-I-0003		45	F	Evd	2	1
ZMapp	19-I-0003		20	M	Evd	2	1
ZMapp	19-I-0003		7	F	Evd	2	1
ZMapp	19-I-0003		60	F	Evd	2	1
ZMapp	19-I-0003		42	M	Evd	7	7
ZMapp	19-I-0003		46	F	Evd	2	1
ZMapp	19-I-0003		21	M	Evd	1	1
ZMapp	19-I-0003		43	F	Evd	4	1
ZMapp	19-I-0003		27	F	Evd	6	4
ZMapp	19-I-0003		25	M	Evd	4	4
ZMapp	19-I-0003		46	F	Evd	1	1
ZMapp	19-I-0003		42	F	Evd	3	1
ZMapp	19-I-0003		18	M	Evd	2	1
ZMapp	19-I-0003		23	F	Evd	3	2
ZMapp	19-I-0003		4	F	Evd	4	1

Study Arm	Subject ID (b) (6)	Age	Sex	Cause of Death	Study Day of Death	Duration of Exposure (Days)
ZMapp	19-I-0003	39	F	Evd	3	1
ZMapp	19-I-0003	6	F	Evd	3	1
ZMapp	19-I-0003	21	M	Evd	2	2
ZMapp	19-I-0003	46	M	Evd	7	4
ZMapp	19-I-0003	4	F	Evd	1	1
ZMapp	19-I-0003	20	M	Evd	6	4
ZMapp	19-I-0003	18	F	Evd	8	7
ZMapp	19-I-0003	67	M	Evd	21	7
ZMapp	19-I-0003	69	F	Evd	3	1
ZMapp	19-I-0003	14	M	Evd	1	1
ZMapp	19-I-0003	3	F	Evd	8	7
ZMapp	19-I-0003	42	F	Evd	1	1
ZMapp	19-I-0003	17	F	Evd	3	1
ZMapp	19-I-0003	31	F	Evd	1	1
ZMapp	19-I-0003	4	F	Evd	3	1
ZMapp	19-I-0003	19	F	Evd	4	2
ZMapp	19-I-0003	62	M	Evd	7	4
ZMapp	19-I-0003	46	M	Evd	3	1
ZMapp	19-I-0003	35	M	Evd	2	1
ZMapp	19-I-0003	19	F	Evd	7	7
ZMapp	19-I-0003	39	F	Evd	4	4
ZMapp	19-I-0003	42	F	Evd	3	2
ZMapp	19-I-0003	50	F	Evd	3	2
ZMapp	19-I-0003	37	M	Evd	3	1
ZMapp	19-I-0003	38	F	Evd	6	4
ZMapp	19-I-0003	47	F	Evd	4	1
ZMapp	19-I-0003	20	F	Evd	1	1
ZMapp	19-I-0003	3	F	Evd	6	5
ZMapp	19-I-0003	32	M	Evd	2	2
ZMapp	19-I-0003	48	F	Evd	2	1
ZMapp	19-I-0003	24	F	Evd	9	7
ZMapp	19-I-0003	22	F	Evd	3	1
ZMapp	19-I-0003	70	M	Evd	8	7
ZMapp	19-I-0003	19	M	Evd	4	1
ZMapp	19-I-0003	25	F	Evd	2	1
ZMapp	19-I-0003	32	M	Evd	1	1
ZMapp	19-I-0003	46	M	Evd	3	2
ZMapp	19-I-0003	22	F	Evd	2	1
ZMapp	19-I-0003	17	F	Evd	1	1
ZMapp	19-I-0003	33	M	Evd	10	7
ZMapp	19-I-0003	20	M	Evd	47	7
ZMapp	19-I-0003	30	M	Evd	18	7
ZMapp	19-I-0003	65	M	Evd	4	4
ZMapp	19-I-0003	50	F	Evd	6	4
ZMapp	19-I-0003	26	M	Evd	5	4
ZMapp	19-I-0003	24	F	Evd	3	1
ZMapp	19-I-0003	15	F	Evd	4	1
ZMapp	19-I-0003	1	F	Evd	6	4
ZMapp	19-I-0003	42	M	Evd	1	1
ZMapp	19-I-0003	27	M	Evd	1	1
ZMapp	19-I-0003	35	F	Evd	1	1
ZMapp	19-I-0003	22	M	Study drug	2	1
ZMapp	19-I-0003	48	M	Evd	3	1

Study Arm	Subject ID	Age	Sex	Cause of Death	Study Day of Death	Duration of Exposure (Days)
ZMapp	19-I-0003 (b) (6)	28	M	Evd	5	4
ZMapp	19-I-0003	33	M	Evd	3	1
ZMapp	19-I-0003	54	F	Evd	2	1
ZMapp	19-I-0003	12	F	Evd	3	1
ZMapp	19-I-0003	39	M	Evd	1	1
ZMapp	19-I-0003	27	F	Evd	2	1
ZMapp	19-I-0003	48	F	Evd	2	2
ZMapp	19-I-0003	17	F	Evd	3	2
ZMapp	19-I-0003	60	F	Evd	1	1
ZMapp	19-I-0003	40	M	Evd	1	1

Source: Analysis by Clinical Data Analyst of adsl.xpt; Software: Python
Abbreviations: ID, identification

Table 63 lists the AEs that lead to death and the causes by preferred term and verbatim term in the ansuvimab-zykl and ZMapp arms. Only one subject in the ansuvimab-zykl died from an SAE of malnutrition. This subject (b) (6) is discussed in detail in Section 7.6.2.

Table 63. List of Adverse Events Leading to Death, Safety Population, PALM Trial

Subject ID	Age	Sex	Preferred Term	Verbatim Term	Study Day of Death	Study Day of AE Onset	Duration of AE*	Duration of Exposure*	Relatedness
Ansuvimab-zykl									
19-I-0003 (b) (6)	28 days	F	Malnutrition	Severe malnutrition	45	44	2	1	Not related
ZMapp									
19-I-0003- (b) (6)	21	M	Vomiting	Vomited aggravated	2	1	2	2	Related
19-I-0003-	21	M	Diarrhoea	Diarrhea aggravated	2	1	2	2	Related
19-I-0003-	22	M	Anaphylactic shock	Anaphylactic shock	2	1	2	1	Related

Source: Analysis by Clinical Data Scientist of adae.xpt; Software: Python
* Duration values are expressed in days.
Abbreviations: AE, adverse event; ID, identification

Subgroup Analysis of Adverse Events

Analyses by race were not conducted because race information was not collected. Analyses of AEs occurring during or post-infusion by sex and age group are presented in Table 64 and Table 65.

Table 64. Subgroup Analysis by Sex for AEs Occuring During or PostInfusion, Safety Population, PALM Trial

	Ansuvimab-zykl (N=173)		Control (N=168)	
Adverse Event	Male N=78	Female N=95	Male N=82	Female N=86
Any AE	33 (42.3)	38 (40)	74 (90.2)	75 (87.2)
Pyrexia	12 (15.4)	18 (18.9)	53 (64.6)	44 (51.2)
Diarrhoea	7 (9)	8 (8.4)	18 (22)	13 (15.1)
Tachypnoea	7 (9)	3 (3.2)	23 (28)	24 (27.9)
Vomiting	7 (9)	7 (7.4)	21 (25.6)	17 (19.8)
Tachycardia	6 (7.7)	9 (9.5)	22 (26.8)	31 (36)
Chills	5 (6.4)	3 (3.2)	33 (40.2)	22 (25.6)
Oxygen saturation decreased	5 (6.4)	1 (1.1)	8 (9.8)	11 (12.8)
Hypotension	4 (5.1)	9 (9.5)	21 (25.6)	31 (36)
Dizziness	2 (2.6)	1 (1.1)	3 (3.7)	2 (2.3)
Dyspnoea	2 (2.6)	4 (4.2)	5 (6.1)	7 (8.1)
Nausea	2 (2.6)	4 (4.2)	7 (8.5)	5 (5.8)
Cerebral malaria	1 (1.3)	0	0	0
Decubitus ulcer	1 (1.3)	0	0	0
Headache	1 (1.3)	2 (2.1)	6 (7.3)	2 (2.3)
Hiccups	1 (1.3)	1 (1.1)	4 (4.9)	0
Hypertension	1 (1.3)	1 (1.1)	10 (12.2)	7 (8.1)
Hypothermia	1 (1.3)	0	2 (2.4)	0
Oedema peripheral	1 (1.3)	0	0	1 (1.2)
Psychotic disorder	1 (1.3)	0	0	0
Seizure	1 (1.3)	0	3 (3.7)	3 (3.5)
Abdominal distension	0	0	1 (1.2)	0
Abdominal pain	0	0	2 (2.4)	3 (3.5)
Abdominal pain upper	0	1 (1.1)	1 (1.2)	2 (2.3)
Agitation	0	1 (1.1)	4 (4.9)	4 (4.7)
Anaphylactic shock	0	0	1 (1.2)	0
Back pain	0	0	1 (1.2)	0
Behaviour disorder	0	2 (2.1)	0	0
Blindness unilateral	0	1 (1.1)	0	0
Bradycardia	0	0	2 (2.4)	3 (3.5)
Chest pain	0	0	3 (3.7)	4 (4.7)
Cough	0	1 (1.1)	2 (2.4)	4 (4.7)
Decreased appetite	0	3 (3.2)	4 (4.9)	2 (2.3)
Dyspepsia	0	1 (1.1)	0	1 (1.2)
Dysphagia	0	0	1 (1.2)	0
Epistaxis	0	0	1 (1.2)	0
Eye pain	0	0	0	1 (1.2)
Feeling hot	0	0	0	1 (1.2)
Flushing	0	0	0	1 (1.2)
Fetal death	0	1 (1.1)	0	1 (1.2)
Haematemesis	0	1 (1.1)	0	1 (1.2)
Haemorrhage	0	1 (1.1)	0	0
Hydrocephalus	0	0	0	1 (1.2)
Malaise	0	0	2 (2.4)	2 (2.3)
Malnutrition	0	1 (1.1)	0	0

	Ansuvimab-zykl (N=173)		Control (N=168)	
	Male	Female	Male	Female
Adverse Event	N=78	N=95	N=82	N=86
Melaena	0	0	0	1 (1.2)
Nasal flaring	0	0	0	1 (1.2)
Oedema	0	0	0	1 (1.2)
Palpitations	0	0	1 (1.2)	0
Pruritus	0	0	2 (2.4)	0
Rash	0	0	1 (1.2)	2 (2.3)
Stevens-Johnson syndrome	0	1 (1.1)	0	0
Umbilical cord short	0	0	0	1 (1.2)
Urethral injury	0	0	1 (1.2)	0

Source: Clinical Data Scientist analysis of adae.xpt and adsl.xpt
All values are expressed as n (%).

Table 65. Subgroup Analysis by Age for AEs Occuring During or Postinfusion, Safety Population, PALM Trial

	Age Groups							
	Ansuvimab-zykl (N=173)				Control (N=168)			
	<6	6-11	12-17	≥18	<6	6-11	12-17	≥18
Adverse Event	N=12	N=19	N=16	N=126	N=14	N=7	N=11	N=136
Any AE	5 (41.7)	8 (42.1)	7 (43.8)	51 (40.5)	11 (78.6)	6 (85.7)	11 (100)	121 (89)
Pyrexia	2 (16.7)	6 (31.6)	1 (6.2)	21 (16.7)	10 (71.4)	4 (57.1)	6 (54.5)	77 (56.6)
Tachycardia	2 (16.7)	4 (21.1)	1 (6.2)	8 (6.3)	3 (21.4)	2 (28.6)	3 (27.3)	45 (33.1)
Diarrhoea	1 (8.3)	1 (5.3)	1 (6.2)	12 (9.5)	3 (21.4)	2 (28.6)	1 (9.1)	25 (18.4)
Hypotension	1 (8.3)	0	1 (6.2)	11 (8.7)	3 (21.4)	1 (14.3)	3 (27.3)	45 (33.1)
Stevens-Johnson syndrome	1 (8.3)	0	0	0	0	0	0	0
Tachypnoea	1 (8.3)	1 (5.3)	1 (6.2)	7 (5.6)	3 (21.4)	3 (42.9)	2 (18.2)	39 (28.7)
Abdominal distension	0	0	0	0	0	0	0	1 (0.7)
Abdominal pain	0	0	0	0	0	0	1 (9.1)	4 (2.9)
Abdominal pain upper	0	0	0	1 (0.8)	0	0	1 (9.1)	2 (1.5)
Agitation	0	0	0	1 (0.8)	1 (7.1)	0	0	7 (5.1)
Anaphylactic shock	0	0	0	0	0	0	0	1 (0.7)
Back pain	0	0	0	0	0	0	0	1 (0.7)
Behaviour disorder	0	0	1 (6.2)	1 (0.8)	0	0	0	0
Blindness unilateral	0	0	0	1 (0.8)	0	0	0	0
Bradycardia	0	0	0	0	0	0	1 (9.1)	4 (2.9)
Cerebral malaria	0	1 (5.3)	0	0	0	0	0	0
Chest pain	0	0	0	0	0	1 (14.3)	0	6 (4.4)
Chills	0	1 (5.3)	0	7 (5.6)	0	3 (42.9)	4 (36.4)	48 (35.3)
Cough	0	1 (5.3)	0	0	0	1 (14.3)	0	5 (3.7)
Decreased appetite	0	0	1 (6.2)	2 (1.6)	0	0	0	6 (4.4)
Decubitus ulcer	0	0	0	1 (0.8)	0	0	0	0
Dizziness	0	0	0	3 (2.4)	0	0	0	5 (3.7)
Dyspepsia	0	0	0	1 (0.8)	0	0	0	1 (0.7)
Dysphagia	0	0	0	0	0	0	0	1 (0.7)
Dyspnoea	0	0	0	6 (4.8)	1 (7.1)	0	0	11 (8.1)
Epistaxis	0	0	0	0	0	0	0	1 (0.7)
Eye pain	0	0	0	0	0	0	1 (9.1)	0
Feeling hot	0	0	0	0	0	0	0	1 (0.7)
Flushing	0	0	0	0	0	0	0	1 (0.7)
Fetal death	0	0	0	1 (0.8)	0	0	0	1 (0.7)
Haematemesis	0	0	0	1 (0.8)	1 (7.1)	0	0	0
Haemorrhage	0	0	0	1 (0.8)	0	0	0	0
Headache	0	0	0	3 (2.4)	0	1 (14.3)	0	7 (5.1)
Hiccups	0	0	0	2 (1.6)	0	0	0	4 (2.9)

	Age Groups							
	Ansuvimab-zykl (N=173)				Control (N=168)			
Adverse Event	<6 N=12	6-11 N=19	12-17 N=16	≥18 N=126	<6 N=14	6-11 N=7	12-17 N=11	≥18 N=136
Hydrocephalus	0	0	0	0	0	0	0	1 (0.7)
Hypertension	0	0	0	2 (1.6)	0	0	1 (9.1)	16 (11.8)
Hypothermia	0	0	0	1 (0.8)	0	0	0	2 (1.5)
Malaise	0	0	0	0	1 (7.1)	0	0	3 (2.2)
Malnutrition	0	0	0	1 (0.8)	0	0	0	0
Melaena	0	0	0	0	1 (7.1)	0	0	0
Nasal flaring	0	0	0	0	0	0	0	1 (0.7)
Nausea	0	0	2 (12.5)	4 (3.2)	0	0	1 (9.1)	11 (8.1)
Oedema	0	0	0	0	0	0	0	1 (0.7)
Oedema peripheral	0	0	0	1 (0.8)	0	0	0	1 (0.7)
Oxygen saturation decreased	0	2 (10.5)	0	4 (3.2)	0	1 (14.3)	2 (18.2)	16 (11.8)
Palpitations	0	0	0	0	0	0	0	1 (0.7)
Pruritus	0	0	0	0	0	0	0	2 (1.5)
Psychotic disorder	0	0	0	1 (0.8)	0	0	0	0
Rash	0	0	0	0	1 (7.1)	0	1 (9.1)	1 (0.7)
Seizure	0	0	0	1 (0.8)	0	0	2 (18.2)	4 (2.9)
Umbilical cord short	0	0	0	0	0	0	0	1 (0.7)
Urethral injury	0	0	0	0	0	0	0	1 (0.7)
Vomiting	0	1 (5.3)	3 (18.8)	10 (7.9)	3 (21.4)	0	4 (36.4)	31 (22.8)

Source: Clinical Data Scientist analysis of adae.xpt and adsl.xpt
All values are expressed as n (%).

Laboratory Findings

Table 66 summarizes changes limited to worsening grade in subjects <18 years of age. Laboratory tests are also reflective of the underlying illness being treated; therefore, the assessment of abnormalities is also highly confounded. The subgroup of subjects <18 years of age was too small to make meaningful comparisons with adult subjects.

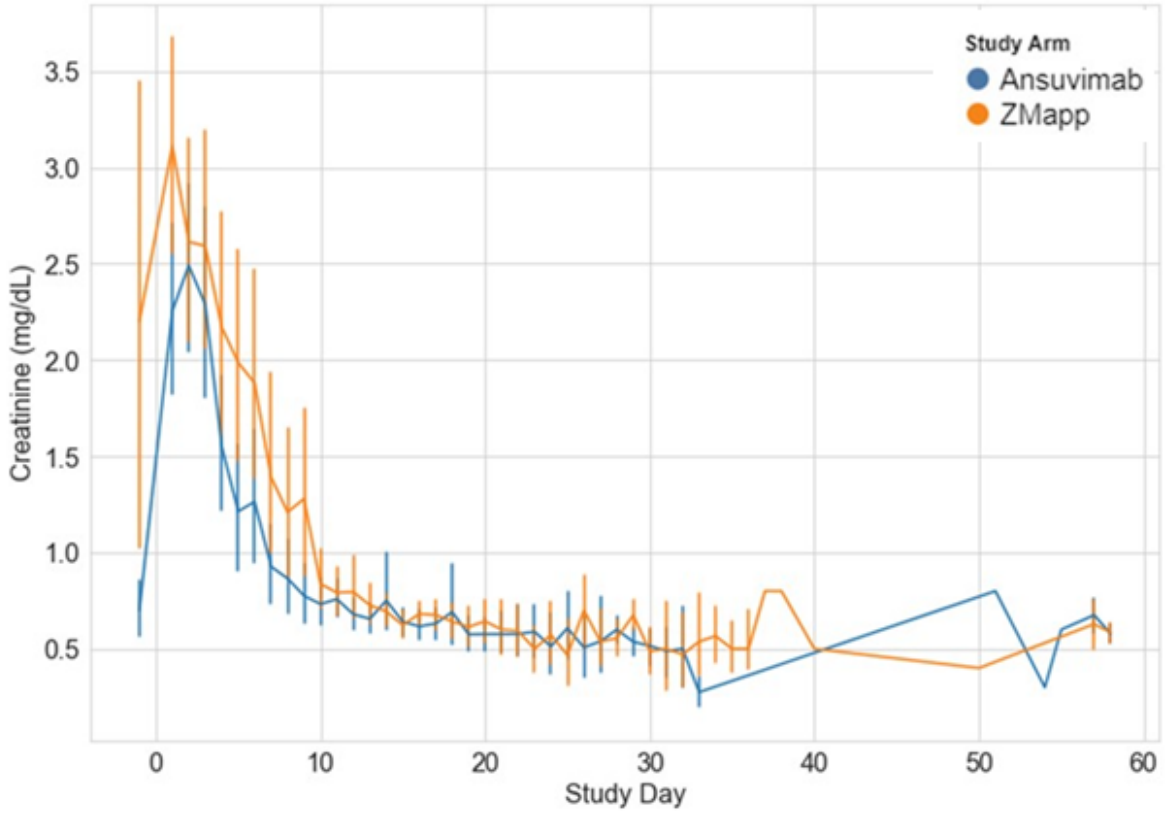
Table 66. Subjects Under 18 Years of Age Meeting Laboratory Abnormality Criteria, Cumulative Worsened Grade From Baseline,[1] Safety Population, PALM Trial

Laboratory Test	Ansuvimab-zykl N=53	ZMapp N=33
Sodium (mmol/L) increased		
Grade 3 or 4 (≥154 mmol/L)	4 (7.5)	3 (9.1)
Sodium (mmol/L) decreased		
Grade 3 or 4 (<125 mmol/L)	4 (7.5)	4 (12.1)
Potassium (mmol/L) increased		
Grade 3 or 4 (≥6.5 mmol/L)	10 (18.9)	7 (21.2)
Potassium (mmol/L) decreased		
Grade 3 or 4 (<2.5 mmol/L)	4 (7.5)	3 (9.1)
Creatinine (mg/dL) increased		
Grade 3 or 4 (>1.8 x ULN or increase to ≥1.5 x baseline)	18 (34)	11 (33.3)
Alanine aminotransferase (U/L) increased		
Grade 3 or 4 (≥5 x ULN)	7 (13.2)	5 (15.2)
Aspartate aminotransferase (U/L) increased		
Grade 3 or 4 (≥5 x ULN)	6 (11.3)	1 (3)

Source: Clinical Data Scientist analysis of adlb.xpt, Software: R
All values are expressed as n (%).
Grading scale used was DAIDS corrected version 2.1.
[a] ULN for serum creatinine =1.2 mg/dL; ULN for alanine aminotransferase =47 U/L; ULN for aspartate aminotransferase =38 U/L.
Abbreviations: N, number of subjects with relevant laboratory data; n, number of subjects with abnormality; ULN, upper limit of normal; PALM, PAmoja TuLinde Maisha.

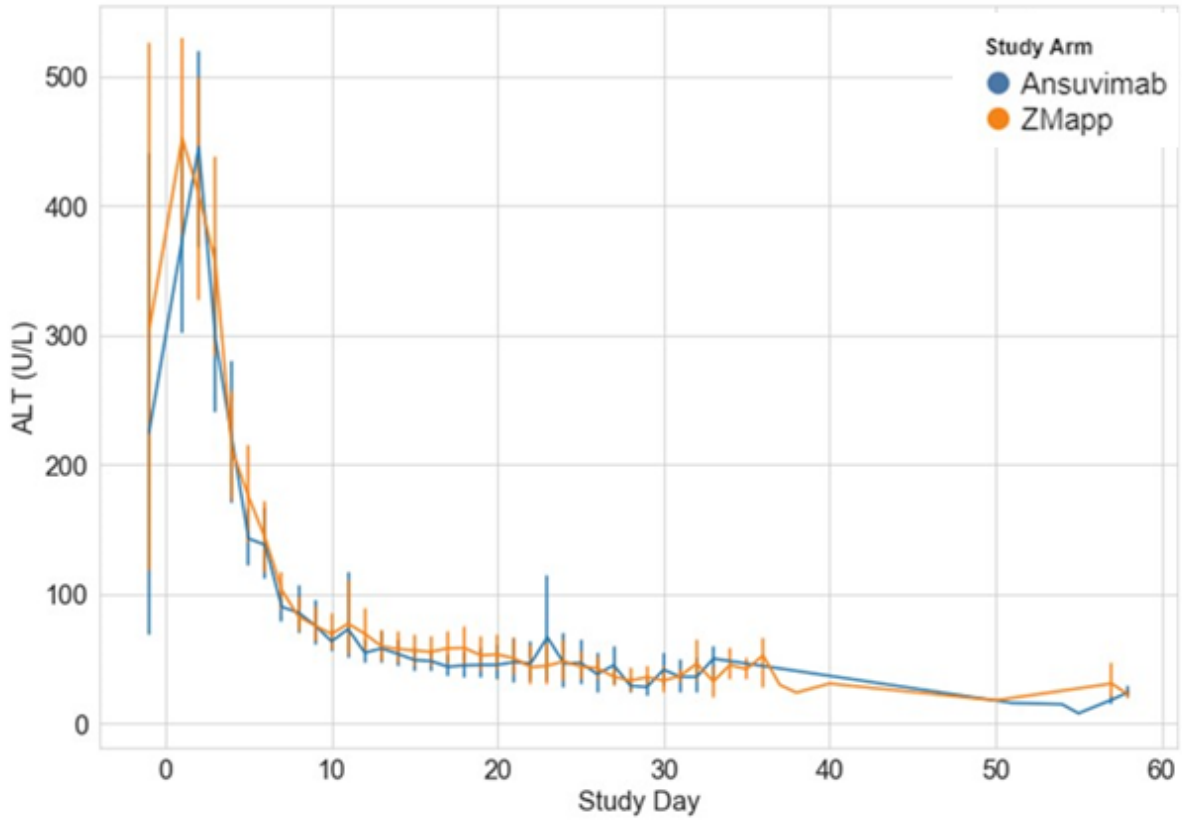
Figures 6, 7, and 8 show the mean daily laboratory values for the ansuvimab-zykl and ZMapp arms from baseline to the end of follow-up in the PALM Trial. Chemistry values (AST, ALT, creatinine) by study day were the prespecified secondary efficacy endpoints. Most of the laboratory values normalized by Day 7, driven by the treatment effect (or lack thereof) of the study drugs. This normalization of laboratory values reflected recovery of renal and hepatic function in survivors. Differences between the treatment arms, however, did not reveal trends suggestive of any safety concern. Erroneous elevated values for Subject (b) (6) on Day 39 in the ZMapp arm were excluded (values on days before and after Day 39 were much lower).

Figure 6. Mean Serum Creatine by Study Day and by Study Arm, Safety Population, PALM Trial



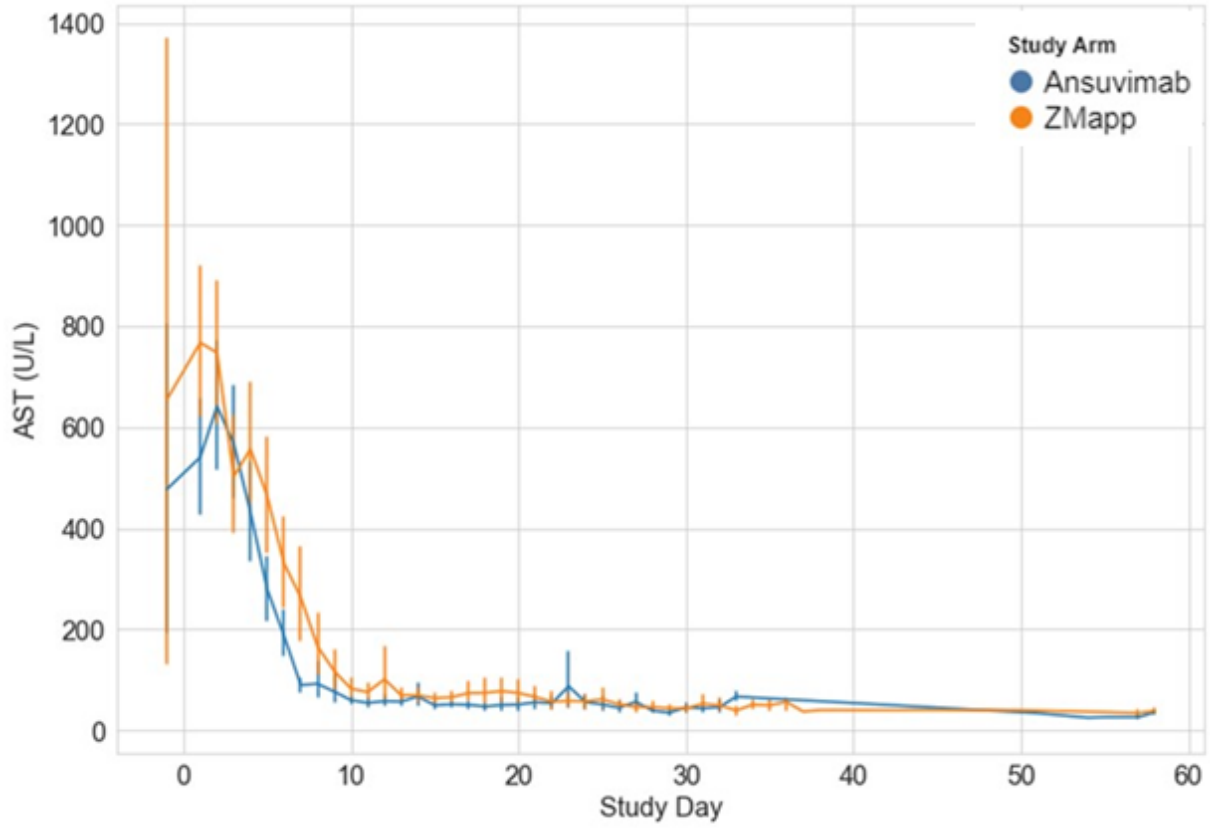
Source: Clinical Data Scientist analysis of adlb.xpt using Python
Note: Erroneous outlier value for Subject (b) (6) on Day 39 in the ZMapp arm was excluded from this figure

Figure 7. Mean Alanine Aminotransferase by Study Day and by Study Arm, Safety Population, PALM Trial



Source: Clinical Data Scientist analysis of adlb.xpt using Python
Note: Erroneous outlier value for Subject (b) (6) on Day 39 in the ZMapp arm was excluded from this figure

Figure 8. Mean Aspartate Aminotransferase by Study Day and by Study Arm, Safety Population, PALM Trial

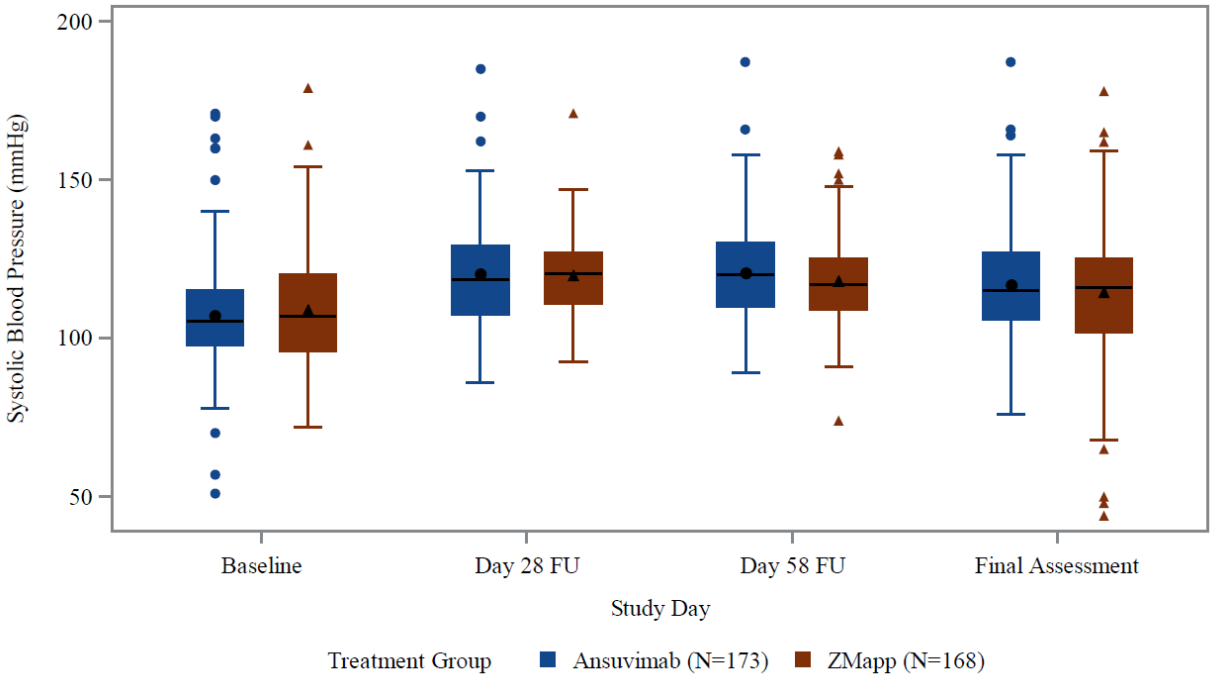


Source: Clinical Data Scientist analysis of adlb.xpt using Python
Note: Erroneous outlier value for Subject (b) (6) on Day 39 in the ZMapp arm was excluded from this figure

Vital Signs

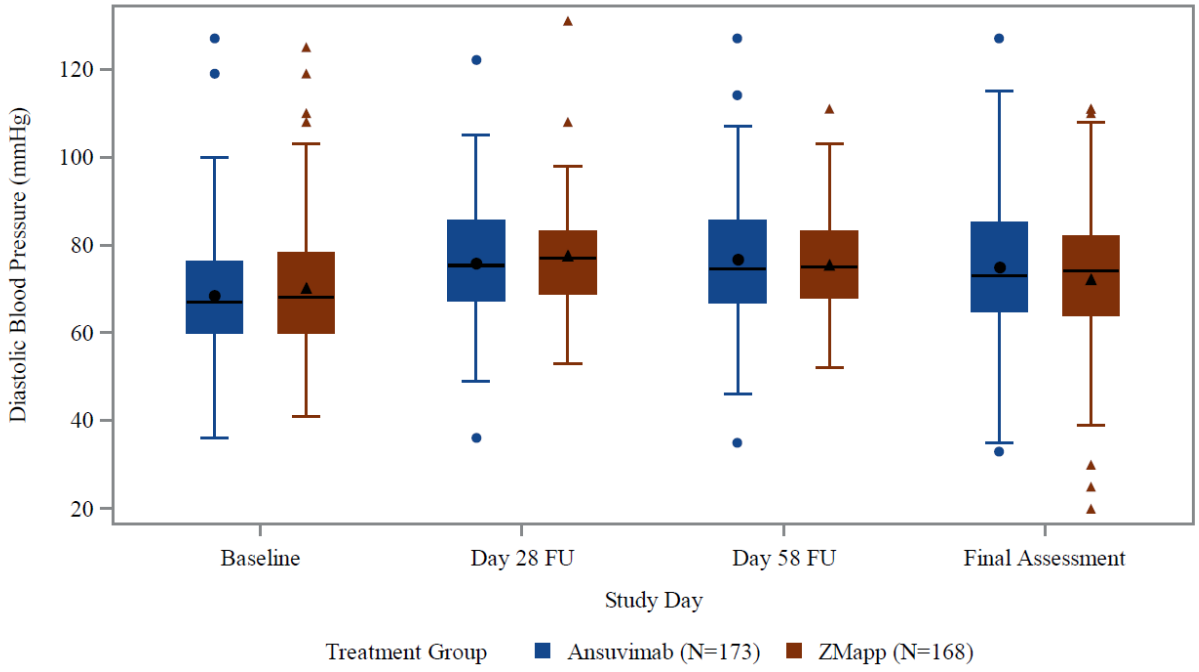
Select vital sign assessments are presented in Figures 9, 10, 11, and 12 for Day 1, Day 28, Day 58, and final assessment by treatment group. Vital signs collected on the same day were averaged for each subject and the daily average are used in the boxplots. Final assessment is the very last assessment for a subject irrespective of study day (hence, if a subject died on Day 2 of the study, then that would be the final assessment). Overall, there was no clinically significant difference in the average vital signs (systolic/diastolic blood pressure, pulse rate, temperature, respiratory rate, and oxygen saturation) reported in both arms at each time point. However, the number of subjects by Day 58 were lower in the control arm compared to the ansuvimab-zykl arm due to the greater proportion of deaths in the control arm.

Figure 9. Boxplots of Systolic Blood Pressure (mmHg), Safety Population, PALM Trial



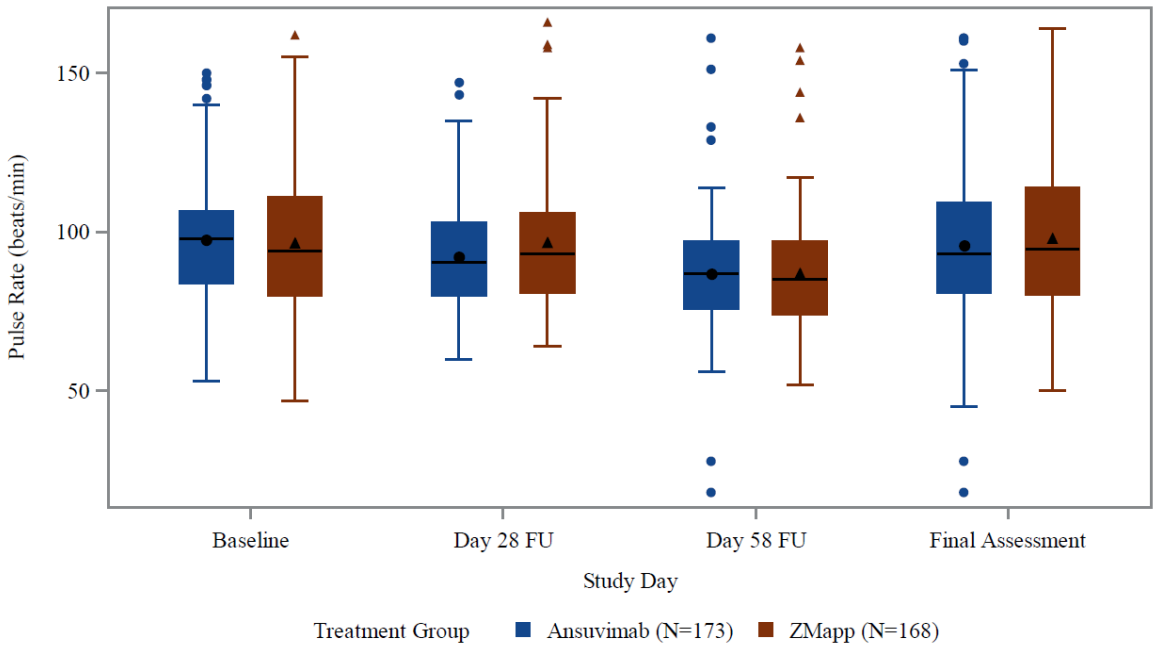
Source: Applicant Clinical Study Report Figure 14.3.5.7 based on data from Table 14.3.5.1

Figure 10. Boxplots of Diastolic Blood Pressure (mmHg), Safety Population, PALM Trial



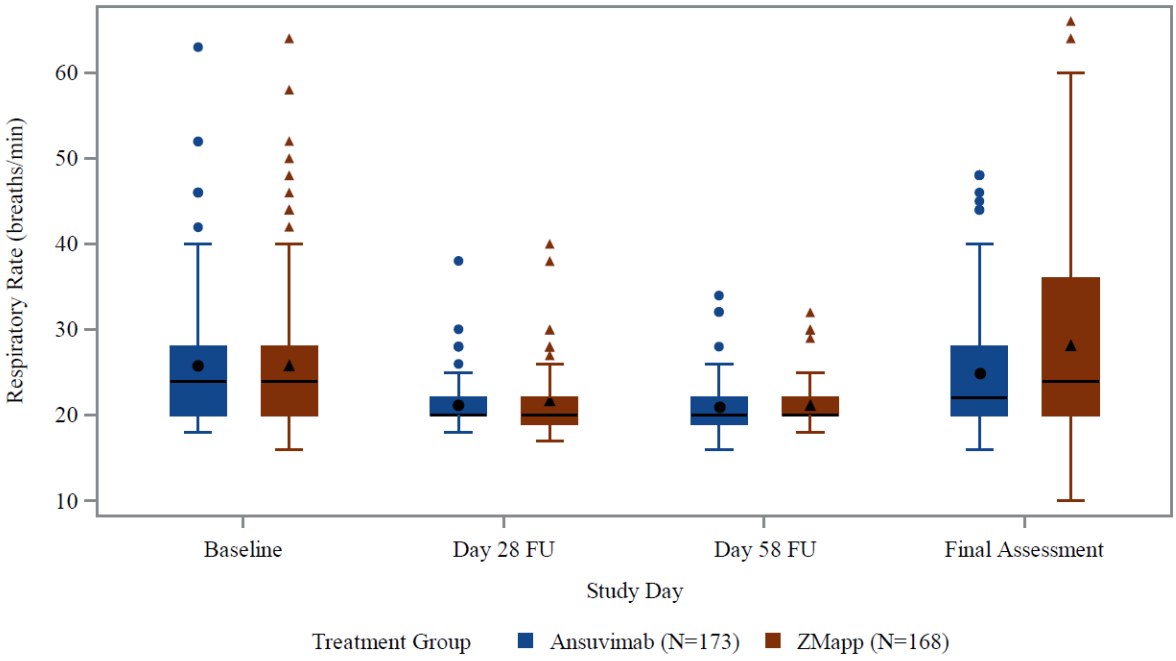
Source: Applicant Clinical Study Report Figure 14.3.5.8 based on data from Table 14.3.5.2

Figure 11. Boxplots of Pulse Rate (Beats/Min), Safety Population, PALM Trial



Source: Applicant Clinical Study Report Figure 14.3.5.9 based on data from Table 14.3.5.3

Figure 12. Boxplots of Respiratory Rate (Breaths/Min), Safety Population, PALM Trial



Source: Applicant Clinical Study Report Figure 14.3.5.11 based on data from Table 14.3.5.5

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

18.1. OND Virology Review

18.1.1. Introduction and Background

The virus family *Filoviridae* is of the *Mononegavirales* order and is comprised of three genera: *Cuevavirus, Ebolavirus*, and *Marburgvirus*. To date, six species of *Ebolavirus* have been identified, including Zaire (EBOV), Sudan, Bundibugyo, Reston, Tai Forest, and Bombali. Filoviruses are negative-strand RNA viruses of which several (EBOV, Sudan, Bundibugyo, and Tai Forest) cause severe hemorrhagic disease characterized by high mortality rates. The virus initially infects monocytes, macrophages, and dendritic cells and spreads systemically to produce a primary viremia that leads to infection of other cell types including vascular endothelial cells. Virus replication leads to a rise in inflammatory cytokine levels and development of coagulopathies resulting in vascular leakage, hypovolemic shock, and multi-organ failure. The mean overall case fatality rate for all known EBOV cases as of this writing is 43.92±0.7% with the two most recent outbreaks recording case fatality rates of 66.0% for the 2018-2020 outbreak in the DRC (3,481 total cases) and 39.5% for the 2013-2016 Western Africa outbreak (28,652 total cases).

EBOV has a linear, single-stranded, negative-sense RNA genome that is ~19 kilobases in length and encodes seven structural proteins and several nonstructural proteins from seven genes (Jacob et al. 2020). Of these EBOV proteins and genes, two are discussed in this review, including the nucleoprotein (NP) gene, which is one of the targets of the RT-PCR assays used to assess EBOV infection and viral load declines over time and the glycoprotein gene and protein. The GP gene is also detected in the RT-PCR assay and is the target of ansuvimab-zykl. EBOV cell tropism is primarily determined by the EBOV GP which interacts with attachment factors on the host cell surface and binds with the Niemann–Pick C1 (NPC1) protein receptor inside the lysosome of infected host cells to initiate fusion and release of the viral genome into the cytoplasm (Jacob et al. 2020).

The EBOV envelope GP constitutes a promising target for antibody-based therapeutics against EBOV because it mediates both viral attachment and fusion with host cells. Blocking GP function with antibodies that bind to the EBOV GP has shown postexposure protection of EBOV-infected nonhuman primates (NHP) with ZMapp when treatment is initiated on Day 5 and subsequent doses administered on Days 8 and 11 after challenge (Qiu et al. 2014). ZMapp is a monoclonal antibody cocktail being developed by LeafBio, Inc. that was used as a control in the PALM Trial and is composed of 3 recombinant mouse/human chimeric IgG1κ mAbs c13C6, c2G4, and c4G7; each of these was derived from 3 mouse mAbs directed against the EBOV Mayinga variant glycoprotein. Ansuvimab-zykl is a single recombinant, human IgG1κ monoclonal antibody that was derived from a human survivor of the 1995 Ebola virus outbreak that occurred in Kikwit, DRC. Ansuvimab-zykl binds to the glycan cap and inner chalice of the EBOV GP1 subunit in an epitope within the receptor binding domain of EBOV where it presumably blocks binding of EBOV GP1 to NPC1 in host cells, inhibiting virus entry into the host cell. In addition, ansuvimab-zykl binds secreted glycoprotein (sGP) and exhibits antibody dependent cellular cytotoxicity (ADCC) activity against cells expressing EBOV GP when

effector cells are added. Treatment of *Zaire ebolavirus* infected rhesus macaques with a single IV dose of ansuvimab-zykl (50 mg per kg) generally protected infected animals from *Zaire ebolavirus*-mediated death when drug was administered 5 days postinfection.

Several studies have indicated that, in general, cocktails of mAbs targeting different EBOV GP epitopes have much greater antiviral activity in the NHP model than individual mAbs used as monotherapy (Olinger et al. 2012; Pettitt et al. 2013; Qiu et al. 2012; Qiu et al. 2013; Qiu et al. 2014)(Table 67).

Table 67. Efficacy of Individual and Combined Monoclonal Antibody Treatments in Guinea Pigs and Nonhuman Primates

Treatment groups, time of treatment	Dose (mg)	Mean time to death (days ± s.d.)	No. survivors/total	Survival (%)	Weight loss (%)	*P* value, compared with	
						cZMAb	MB-003
Guinea pigs						–	–
PBS, 3 dpi	N/A	7.3 ± 0.5	0/4	0	9%	–	–
cZMAb, 3 dpi	5	11.6 ± 1.8	1/6	17	7%	–	–
MB-003, 3 dpi	5	8.2 ± 1.5	0/6	0	40%	–	–
ZMapp1, 3 dpi	5	9.0 ± 0.0	4/6	67	<5%	0.190	0.0147
ZMapp2, 3 dpi	5	8.3 ± 0.6	3/6	50	8%	0.634	0.0692
ZMapp3, 3 dpi	5	8.6 ± 1.1	1/6	17	9%	0.224	0.411
c13C6, 1 dpi	5	8.4 ± 1.7	1/6	17	9%	–	–
h13F6, 1 dpi	5	10.2 ± 1.8	1/6	17	21%	–	–
c6D8, 1 dpi	5	10.5 ± 2.2	0/6	0	38%	–	–
Nonhuman primates							
PBS, 1 dpi	N/A	8.4 ± 1.9	0/1	0			
MB-003, 1 dpi	50	14.0 ± 2.8	1/3	33			
c13C6, 1 dpi	50	9.0 ± 1.4	1/3	33			
h13F6, 1 dpi	50	9.0 ± 2.0	0/3	0			
c6D8, 1 dpi	50	9.7 ± 0.6	0/3	0			

Source: Table 1 from Qiu et al. (Qiu et al. 2014)

A cocktail comprised of two or more mAbs is thought to confer protection via complementary mechanisms involving neutralization and neutralization-independent mechanisms, and may reduce the opportunity for selection of escape mutants (Murin et al. 2014). In addition, the positioning of the epitope on the GP structure will likely determine if a particular mAb is neutralizing. For EBOV, antibodies against the mucin-like domains of the GP are generally non-neutralizing because these domains, as well as any antibodies bound to them, are stripped from the viral surface by host cathepsins in the endosome, leaving behind an antibody-free, functional receptor-binding core of GP (Murin et al. 2014).

An important consideration for mAb cocktails is whether or not one or more of the mAbs bind to sGP. sGP is the soluble, dimeric version of GP that results from the primary open reading of the *GP* gene and is expressed abundantly during EBOV infection (Sanchez et al. 1998). An insertion/deletion in the EBOV GP gene sequence is known to arise in the viral population after passage in cell culture resulting in an insertion of a uridine at the poly-U site at position 6918 to 6924, shifting it from a 7U to an 8U genotype. This change occurs within 24 hours postinfection in cell culture and, as a result, flips the normal production ratios of sGP:GP such that GP is now the dominant product made with the 8U genotype (Kugelman et al. 2012; Volchkov et al. 1995). Importantly, mAbs that bind sGP may not be as effective in protecting against infection, because sGP could serve as a decoy for mAbs that might otherwise bind viral particles (Murin et al. 2014). Of note, ansuvimab-zykl binds to sGP.

18.1.1.1. Important Milestones in Product Development

Initial Development Under the Animal Rule

Given the challenges of conducting adequate and well-controlled clinical trials for treatment of EBOV infection, the development program for ansuvimab-zykl was initially based on fulfilling criteria for potential approval by the Animal Rule pathway. When the 2018 eastern DRC outbreak occurred, the nonclinical program was progressing but was incomplete. However, the NHP data were sufficient to provide proof-of concept for antiviral activity against EBOV infection and use of a single 50 mg/kg IV dose of ansuvimab-zykl in the clinical trials described below (PALM Trial and EAP). The NHP studies (rhesus macaques infected with EBOV) demonstrated improved survival of animals treated with single doses of 30 mg/kg and 50 mg/kg compared to placebo.

The 50 mg/kg dose was selected as the clinical dose for treatment of patients infected with EBOV to potentially overcome the variability of baseline viral load in patients infected with EBOV, and a high risk of death. Based on pharmacokinetic data from study NIH-18-I-0069 (VRC608; NCT03478891) conducted in healthy human volunteers, the mean serum half-life of ansuvimab-zykl was ~24 days and there was low pharmacokinetic variability among study participants (Gaudinski et al. 2019). Compared to PK levels in NHPs dosed with 50 mg/kg, the C_{max} of the 50 mg/kg group in humans was approximately 1.4-fold greater, indicating that the exposure of ansuvimab-zykl in humans at this dose would likely exceed the exposure observed with the 30 and 50 mg/kg doses assessed in infected rhesus macaques. In addition, the 50 mg/kg dose was the highest dose evaluated in healthy human volunteers, and no serious or concerning safety issues were identified (Gaudinski et al. 2019).

***Zaire ebolavirus* Outbreak in 2018**

On August 1, 2018, the Ministry of Health of the DRC reported an outbreak of Ebola virus disease in the North Kivu province (Centers for Disease Control and Prevention 2018). It was subsequently determined to be caused by a variant of the *Zaire ebolavirus* species. Cases were also reported in the Ituri and South Kivu provinces of DRC. At the time the outbreak was reported, confirmed and probable cases had been reported in twenty-nine health zones of the North Kivu, South Kivu, and Ituri provinces of DRC. This outbreak was declared over on June 25, 2020. In total, 3,481 cases (probable and confirmed) of EBOV infection were reported, with 2,299 deaths. It was the 10th and largest EBOV outbreak in the DRC, and the second largest outbreak of EBOV ever recorded since the virus was discovered in 1976 in the DRC (World Health Organization 2019).

The PALM Ebola Therapeutics Clinical Trial (19-I-0003, NCT03719586)

The PAmoja TuLinde Maisha (Kiswahili for “Together Save Lives”) Ebola Therapeutics Trial was a 4-arm, 1:1:1:1 randomized, controlled clinical trial comparing a control arm of ZMapp to three newer investigational agents: 1) remdesivir, a nucleotide analogue EBOV RNA-polymerase inhibitor, 2) ansuvimab-zykl, a single investigational human monoclonal antibody directed against a highly conserved region in the *Zaire ebolavirus* receptor-binding domain of the envelope glycoprotein that was identified from a survivor of the 1995 *Zaire ebolavirus* outbreak in Kikwit, DRC, and 3) REGN-EB3, a formulated cocktail of three fully human

recombinant IgG1 monoclonal antibodies against three noncompeting epitopes on the envelope glycoprotein of *Zaire ebolavirus*.

ZMapp was used as the control arm in the PALM Trial rather than optimized standard of care alone, as it was widely endorsed that it would be unethical to randomize patients to receive no putative antiviral therapies. The protocol originally opened as a three-arm trial in November 2018 comparing remdesivir and ansuvimab-zykl to ZMapp, with REGN-EB3 added as a 4th arm in January 2019.

A total of 681 patients were enrolled between November 20, 2018 and August 9, 2019 at which time the DSMB recommended stopping the PALM RCT and that randomization to the ZMapp and remdesivir arms be stopped. The DSMB further recommended that all future patients be randomized to the ansuvimab-zykl or REGN-EB3 arms in an extension phase. These recommendations were based on an interim analysis of 499 participants enrolled in the RCT, which revealed that REGN-EB3 crossed an early monitoring boundary for efficacy over ZMapp. The DSMB also noted that ansuvimab-zykl was close to crossing an early monitoring boundary for efficacy relative to ZMapp. Furthermore, the mortality rates for REGN-EB3 and ansuvimab-zykl were not statistically significantly different, justifying the continued randomization to these two therapies. At the time of the DSMB recommendation, at 28 days, death had occurred in 61 of 174 patients (35.1%) in the ansuvimab-zykl group, as compared with 83 of 168 (49.4%) in the ZMapp group (P=0.008) (Mulangu et al. 2019).

Of note, there were more than 2,900 confirmed or suspected cases of *Zaire ebolavirus* infection reported in the DRC as of August 2019, when the DSMB recommendation was made, with an overall case fatality rate of 67%. The final PALM RCT cohort included 681 participants, the number enrolled up until the DSMB recommendation. Based on FDA efficacy analysis, the numbers and rates observed for ansuvimab-zykl showed an overall mortality rate of 35.1% (61 of 174 patients died), while the mortality rate for patients who had high baseline viral loads (CtNP ≤22) was 69.9% (51/73) and was 9.9% (10/101) for patients who had lower baseline viral loads (CtNP >22).

Monitored Emergency Use of Unregistered and Investigational Interventions Expanded Access Program

The INRB was designated by the DRC Ministry of Health as the lead research coordinator for the EBOV outbreak. The EBOV Treatment Units (ETUs) were staffed by medical personnel from humanitarian nongovernmental organizations under the auspices of the Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) framework which established ethical and quality standards. On August 27, 2018, the MEURI committee recommended the following investigational products for expanded access use based on available nonhuman and human data: ZMapp, remdesivir, REGN-EB3, and ansuvimab-zykl (World Health Organization 2018). Among the 251 patients assigned a single patient protocol number for treatment with ansuvimab-zykl under this EAP, all were treated with ansuvimab-zykl under MEURI at 7 ETU locations (Beni, Butembo, Katwa, Mangina and Komanda, Chowe CS, and Goma) in one country (DRC).

The ETU sites were managed by different nongovernmental organizations and included Alliance for International Medical Association, Médecins Sans Frontières, WHO, International Medical Corp, and Samaritan's Purse. ETU sites in Butembo and Katwa were managed by both Médecins

Sans Frontiéres and WHO at different times. The greatest number of patients were treated at the Butembo site followed by the Beni and Mangina sites. The majority of patients (167, 66.5%) were discharged from the ETU. A total of 81 (32.3%) patients died, and the outcome of 4 patients was pending at the time of the data cut-off.

18.1.1.2. Methodology

Reverse Transcriptase Polymerase Chain Reaction

The Cepheid GeneXpert RT-PCR assay was used to document positive EBOV infection for enrollment into the PALM clinical trial and to assess EBOV viral load at baseline and at various timepoints in Study 19-I-0003 (PALM RCT). The Cepheid GeneXpert assay is a real-time 2-target RT-PCR assay intended for the qualitative detection of RNA from *Zaire ebolavirus*. The assay separately quantifies the GP and NP genes of EBOV with results reported as cycle threshold and with an upper Ct level of 45 for both genes.

Viral load (i.e., the number of copies of RNA/mL) and Ct are inversely correlated because greater concentrations of virus are detected in fewer cycles. Thus, a high Ct value from NP amplification (CtNP) denotes low viral load, and a low Ct value denotes high viral load (CtNP ≤22: high viral load and CtNP >22: low viral load). For reference, the Applicant stated that a CtNP ≤22 is equivalent to 7 $\log_{10}$ RNA copies/mL and higher, and a CtNP >22 is equivalent to less than 7 $\log_{10}$ RNA copies/mL. The RT-PCR assay for EBOV reports both CtNP and CtGP; however, because the assay is more sensitive to the NP target, CtNP was used in all analyses. (b) (5)

(b) (5)

Conservation of Ansuvimab-zykl Epitope

A bioinformatics investigation was performed to assess the genetic diversity of the EBOV GP region that ansuvimab-zykl binds (111-LEIKKPDGS-119) using 569 virus genome sequences from subjects of epidemiologic interest during the Ebola virus disease outbreak in the North Kivu province of the DRC, which has infected over 3000 people since it was first identified in August of 2018. There were 50 positions in subsequent EBOV isolates that had amino acid changes (relative to the initial EBOV Ituri variant), representing an additional 49 unique EBOV GP Ituri variants. One of these substitutions, GP_L111I, occurred at a position that is part of the ansuvimab-zykl epitope. Of note, 12 substitutions were detected in the EBOV sequences from two or more subjects, but none of these positions were proximal to the ansuvimab-zykl epitope and the Applicant reported that none of these substitutions were with 10 Angstroms of residues of the ansuvimab-zykl epitope.

Phenotypic Analysis of Substitutions

Phenotypic analyses of select EBOV substitutions were performed using EBOV Makona GP VLPs generated by cotransfecting HEK293T cells with a mix of plasmid constructs expressing EBOV Mayinga GP (wild-type or variant of interest), HIV Gag-Pol, and an HIV proviral vector encoding for firefly luciferase.

18.1.1.3. Prior FDA Virology Reviews

A total of 16 Clinical Virology reviews were written for ansuvimab-zykl during the IND development phase from February 22, 2018 to July 2, 2020.

18.1.1.4. Major Virology Issues That Arose During Product Development

No Human Dose Optimization Studies Were Conducted for Ansuvimab-zykl

Lower efficacy was observed in subjects treated with ansuvimab-zykl in the PALM RCT who presented with high baseline EBOV viral loads (CtNP ≤22) compared to subjects with lower baseline viral load (CtNP >22), but it is unknown whether a higher dose could potentially reduce mortality for those with high baseline EBOV viral loads. A concern related to dose optimization is the potential for EBOV sGP that circulates at concentrations of 100- to 1000-fold higher than EBOV particles in the serum of infected humans (Cook and Lee 2013; de La Vega et al. 2015; Sanchez et al. 1996) to interfere with ansuvimab-zykl and reduce the overall efficacy of the mAb.

The Applicant provided nonclinical data showing that the ansuvimab-zykl binding epitope lies within a region of EBOV GP that would allow it to bind to sGP with similar affinity as it binds to GP (Section 18.1.2.1). A higher dose of ansuvimab-zykl may improve efficacy by increasing the concentration of this mAb available to interact with sGP and GP in the viral particles of infected patients. Of note, the nonclinical virology development program for ansuvimab-zykl is incomplete, as the approval of this product was accelerated due to an opportunity to assess this product in an emergency outbreak setting in the DRC. The impact of sGP binding to ansuvimab-zykl has not been adequately addressed.

Conclusion. A clinical PMC will be communicated to the Applicant asking them to commit to conducting a clinical trial to assess higher doses of ansuvimab-zykl.

The Development of Resistance Against Ansuvimab-zykl has Not Been Adequately Characterized

The Applicant provided insufficient nonclinical and clinical data to assess the durability of ansuvimab-zykl as a treatment for EBOV. Limited studies have been performed to identify resistance pathways for ansuvimab-zykl, and no studies have been performed in clinical trials or relevant animal models to assess resistance. Amino acid substitutions associated with reduced susceptibility of ansuvimab-zykl have not been identified to date. Of note, the nonclinical virology development program for ansuvimab-zykl is incomplete, as the approval of this product was accelerated due to an opportunity to assess this product in an emergency outbreak setting in the DRC. No cell culture resistance selection data have been provided to date.

Conclusion. Three resistance related PMRs will be communicated to the Applicant to address this deficiency.

18.1.1.5. State of Antivirals Used for the Indication Sought

The U.S. Food and Drug Administration approved Inmazeb (atoltivimab, maftivimab, and odesivimab-ebgn), a 1:1:1 mixture of three monoclonal antibodies, as the first FDA-approved treatment for *Zaire ebolavirus* infection in adult and pediatric patients on October 14, 2020. Of note, this cocktail was approved based on the same clinical trial used to support this application.

18.1.2. Nonclinical Virology

Ansuvimab-zykl is a recombinant, fully human, gamma immunoglobulin type 1 (IgG1) mAb that targets the *Zaire ebolavirus* glycoprotein, preventing EBOV entry into cells. The majority of the nonclinical virology development program has been described in two publications (Corti et al. 2016; Misasi et al. 2016), and data from these manuscripts will be reviewed below where appropriate.

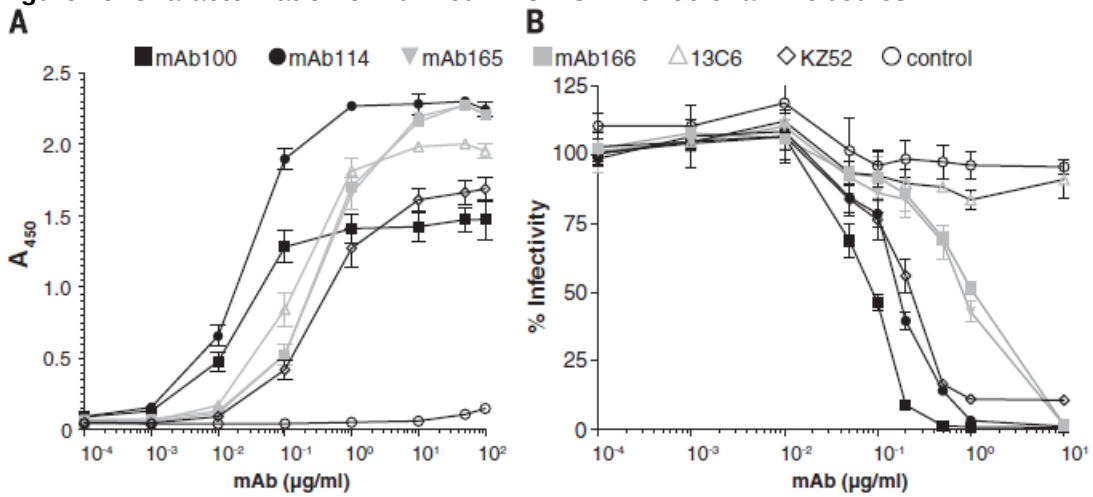
18.1.2.1. Mechanism of Action

Ansuvimab-zykl was derived from a monoclonal antibody isolated from the peripheral blood mononuclear cells of a subject who survived the 1995 Ebolavirus outbreak in Kikwit, DRC and maintained circulating antibody for more than 10 years after infection (Corti et al. 2016). Ansuvimab-zykl was selected following isolation and screening of a panel of memory B-cells based on its binding to the *Zaire ebolavirus* GP and neutralization potential (Corti et al. 2016). Briefly, blood was obtained from two survivors of the 1995 EBOV outbreak in Kikwit, Democratic Republic of the Congo, 11 years after infection. GP-specific antibodies were assessed by ELISA.

The reciprocal 10% maximal binding EC_{90} titer (the reciprocal dilution at which there is a 90% decrease in antigen binding) for the subject who was more severely ill (Subject 1) was 2326, higher than control sera by more than a factor of 10, and serum from this subject displayed virus neutralizing activity (see Section 18.1.2.2 below). Memory B cells from this subject's peripheral blood mononuclear cells and immortalized individual clones were immortalized with Epstein-Barr virus. Forty clone supernatants displayed a range of GP binding and two of these, mAb100 and mAb114, exhibited markedly higher neutralizing activity than all other mAbs (Corti et al. 2016). Two additional GP-specific clones were rescued, identified as mAb165 and mAb166. mAb100, mAb114, mAb165, and mAb166 mRNA sequences were amplified by RT-PCR and monoclonal antibodies were produced by transient transfection. mAb114 was given the name ansuvimab-zykl during development.

ELISA was used to assess binding of all four of these mAbs to EBOV GP (Mayinga variant), and ansuvimab-zykl displayed maximal binding nearly 50% higher than that of KZ52 (Maruyama et al. 1999), a prototypic EBOV GP–specific human mAb, and 25% higher than that of 13C6, a component of the ZMapp cocktail (Corti et al. 2016; Wilson et al. 2000). Ansuvimab-zykl exhibited half-maximal binding (IC_{50} value) at a concentration of 0.02 µg/mL, which was lower than the values reported for other mAbs by a factor of 7 to ~17. KZ52 and 13C6 had IC_{50} values of 0.33 µg/mL and 0.14 µg/mL, respectively (Corti et al. 2016)(Figure 13-A). Neutralization of pseudotyped EBOV GP (Mayinga variant) lentivirus particles, which was part of the mechanism of action screening, is shown in Figure 13-B.

Figure 13. Characterization of Purified EBOV GP Monoclonal Antibodies

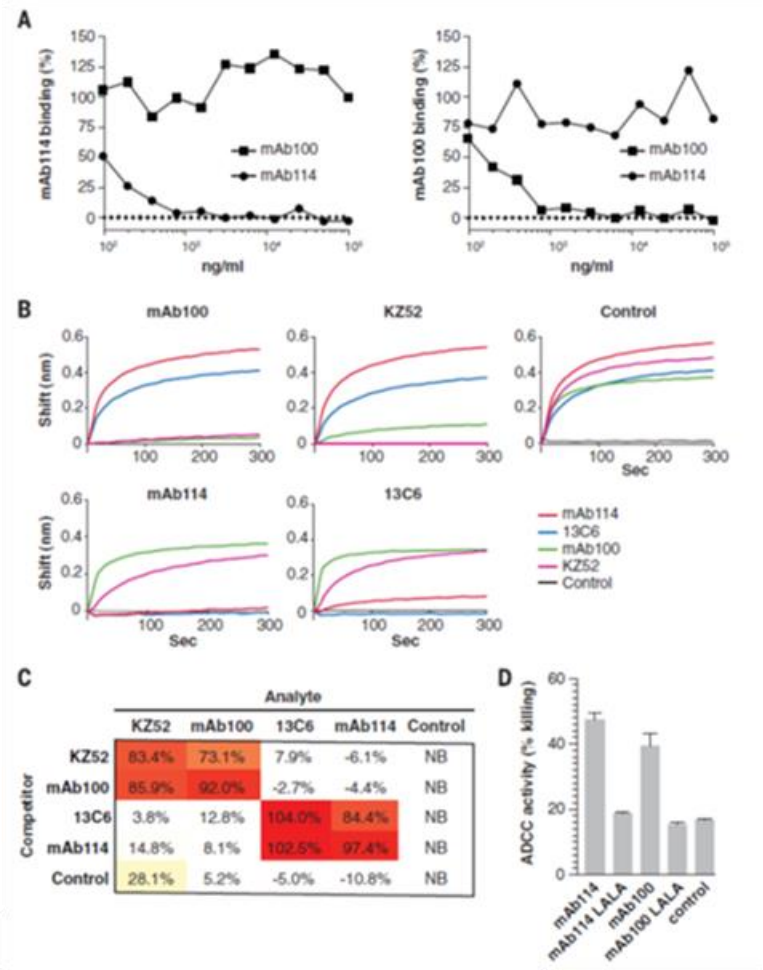


Source: Figure 2 from Corti et al. (Corti et al. 2016)
A. EBOV GP ELISA in the presence of purified mAbs as indicated: A_{450}, mean ± SD (n=3, representative experiment shown).
B. Pseudotyped EBOV GP lentivirus particles were incubated with increasing amounts of purified mAbs and infection of HEK293Tcells determined as in Fig. 1B of source. Percent infectivity = [(RLU with ant body)/(RLU without antibody)] × 100%, mean ± SD (n=3, representative experiment shown).
Abbreviations: mAb114, ansuvimab-zykl

Ansuvimab-zykl variable heavy chain and variable light chain genes were cloned by PCR into human Igγ1 expression vectors and produced by stable transfection into a CHO cell line in accordance with current good manufacturing practice regulations. The authors reported that the presence of additional substitutions on either the variable heavy chain or variable light chain was required to achieve the level of the fully matured ansuvimab-zykl binding (Corti et al. 2016). These results indicate a rapid pathway of ansuvimab-zykl affinity maturation through one or two somatic mutations, which became redundant as further mutations accumulated, a finding that the authors stated was reminiscent of what was recently observed for the generation of broadly neutralizing influenza antibodies (Corti et al. 2016). The fragment crystallizable region (Fc) was not modified.

To define the regions targeted by mAb100 and ansuvimab-zykl, the authors used biolayer interferometry to assess GP binding in competition with mAbs, KZ52 and 13C6, which have epitopes in the GP base and glycan cap, respectively (Lyon et al. 2014; PREVAIL II Writing Group 2016). The results indicated that ansuvimab-zykl recognizes (at least in part) the glycan cap region, as demonstrated by competition with 13C6 (Figure 14).

Figure 14. Binding Regions and Effector Function



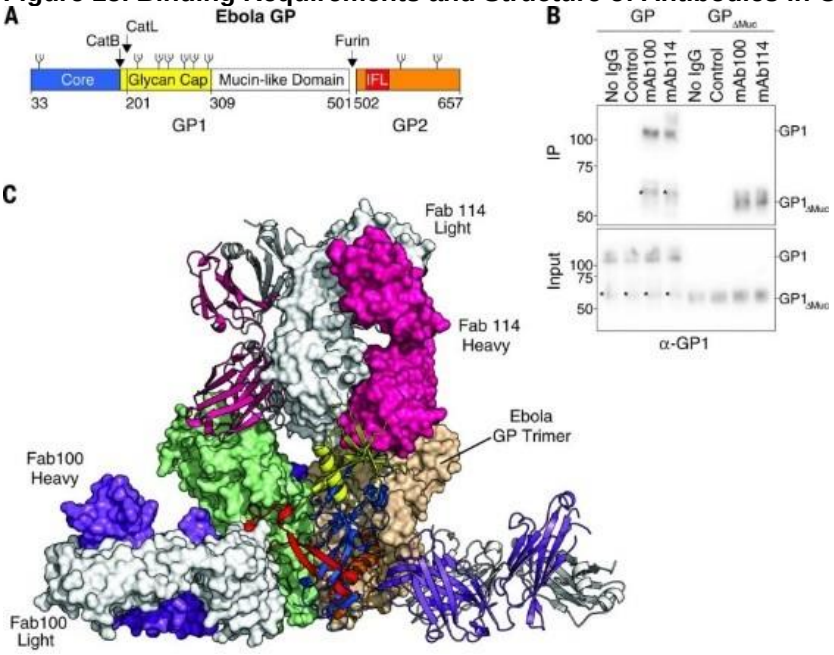
Source: Figure 3 from Corti et al. (Corti et al. 2016)
A. Inhibition of binding of biotinylated mAb114 (left) and mAb100 (right) to GP-expressing MDCK-SIAT cells by pre-incubation with increasing amounts of homologous or heterologous unlabeled antibodies. Shown is the percentage binding of biotinylated ant body (n=1).
B and C. Biolayer interferometry competitive binding assay to soluble EBOV GP using mAb100, mAb114, KZ52, 13C6, and isotype negative control. Biosensors were preloaded with GP followed by the competitor and analyte antibodies as indicated. Analyte binding curves B and quantitated percent inhibition C are reported (n=3, representative experiment shown).
D. Antibody-dependent cell-mediated cytotoxicity (ADCC) assay was determined for mAb100, mAb114 (n=3, representative experiment shown), control antibody, or derivative antibodies with LALA mutations that abrogate Fc-mediated killing of HEK293Tcells (n=1), all at 31.6 ng/ml. ADCC activity is shown as mean ± SD.
Abbreviations: mAb114, ansuvimab-zykl

Ansuvimab-zykl binds EBOV GP without the mucin domain with a K_D of 0.2nM at pH 7.4 and 0.6nM at pH 5.3 as measured by biolayer interferometry (Corti et al. 2016).

Because some EBOV GP antibodies are reportedly able to mediate ADCC (Olinger et al. 2012), the authors assessed the ADCC activity of ansuvimab-zykl in a flow cytometric assay (Figure 14-D). The authors reported that ansuvimab-zykl mediated ADCC with maximal activity observed at a mAb concentration of 30 µg/mL. According to the authors, target cell killing was mediated through Fc receptors, because mAbs containing the so called LALA substitutions (Fc substitutions L234A and L235A) abrogated ADCC activity (Hezareh et al. 2001). Therefore, the authors concluded that these mAbs have the potential to induce a key viral clearance mechanism by directly killing infected cells.

To further characterize the mechanism of action, co-immunoprecipitation and X-ray crystallography studies were performed to identify the structural and molecular basis of neutralization for mAb100 and ansuvimab-zykl. The authors stated that the GP1 subunit contains a core domain and a "glycan cap," which are shielded by the heavily glycosylated mucin-like domain (MLD) (Figure 15-A). The MLD is dispensable for virus entry but is a target for host antibody responses. The immunoprecipitation assay results showed that ansuvimab-zykl recognized GP ectodomains lacking the MLD ($GP_{\Delta Muc}$), indicating that the epitopes for these mAbs were elsewhere on GP (Figure 15-B). To identify the epitopes recognized by ansuvimab-zykl, a crystal structure of the antigen-binding fragment (Fab114) was determined individually to 2.0 Å, and the complex structure was solved by molecular replacement using the refined structures of the unbound Fabs and the previously solved EBOV $GP_{\Delta Muc}$ structure (Wilson et al. 2000) as search models. The crystal structure showed that Fab114 (ansuvimab-zykl) binds within the GP chalice, perpendicular to the viral membrane, and makes contacts with the glycan cap and the GP1 core (Figure 15-C) (Misasi et al. 2016). The primary epitope targeted by ansuvimab-zykl is linear and comprised of GP amino acid residues 111-LEIKKPDGS-119 (Misasi et al. 2016).

Figure 15. Binding Requirements and Structure of Antibodies in Complex With GP



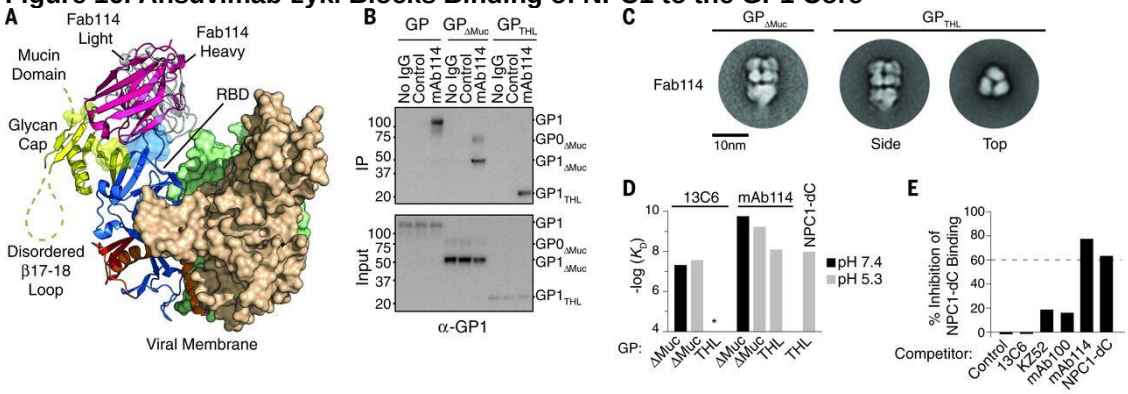
Source: Figure 1 from (Misasi et al. 2016)
A. Schematic representation of GP monomer colored by domain. GP1 core region (33 to 190) is colored blue, GP1 glycan cap is colored yellow (201 to 308), and the mucin-like domain is uncolored (309 to 501). The GP2 IFL is colored red, and the remainder of GP2 is colored orange. Glycans are shown as branched lines, and proteolytic cleavage sites are labeled with arrows. Disulfide bonds within and between GP1 and GP2 are omitted for clarity.
B. IP of soluble GP ectodomain containing or lacking the mucin-like domain ($GP_{\Delta Muc}$) by mAb100, mAb114, or isotype control. Binding and input were analyzed using immunoblotting for GP1. *GP1 degradation product present only in mucin-containing GP. n=3 replicates; representative image shown.
C. Crystal structure of $GP_{\Delta Muc}$ in complex with Fab100 and Fab114. Fab100 is shown in purple (heavy chain) and white (light chain). Fab114 is shown in pink (heavy chain) and white (light chain). Molecular surfaces of two $GP_{\Delta Muc}$ protomers are colored in green and beige, whereas the third is shown as a ribbon representation and colored according to the schematic in (A).
Abbreviations: Fab114 and mAb114, ansuvimab-zykl

Biochemical studies have shown that EBOV entry requires cleavage by cathepsins L and B, which occurs in the endosome and releases the glycan cap and MLD, exposing the receptor-

binding domain (RBD) within the GP1 core (Misasi et al. 2016) and references contained therein). The authors used an immunoprecipitation assay to show that ansuvimab-zykl interacts with GP ectodomains lacking the MLD ($GP_{\Delta Muc}$) and a recombinant GP protein that cleaved in a manner consistent with cathepsin cleavage (GP_{THL}) (Figure 16-B).

To determine if ansuvimab-zykl binds to GP that has been cleaved by cathepsins and prevents interaction of the RBD with the NPC1 receptor, the authors performed a competition assay with ansuvimab-zykl, GP_{THL}, and NPC1 domain C (NPC1-dC; representing the domain responsible for engaging cleaved GP and mediating virus entry) using biolayer interferometry. The results indicated that when ansuvimab-zykl was bound to GP_{THL}, NPC1-dC was unable to bind (Figure 16-E). Similar results were obtained using immunoprecipitation (data provided but not shown). These findings are consistent with the observation that both Fab114 (ansuvimab-zykl) and NPC1-dC have similar affinities for GP_{THL} (Figure 16-D) and indicate that ansuvimab-zykl neutralizes EBOV infection by preventing binding of cathepsin-cleaved GP to its receptor NPC1.

Figure 16. Ansuvimab-zykl Blocks Binding of NPC1 to the GP1 Core



Source: Figure 4 from (Misasi et al. 2016)
A. Fab114 binds to regions in the glycan cap and core of GP1. The variable domain of a single Fab114 is shown in ribbons, and all other Fabs have been removed for clarity. GP residues predicted to contact Fab114 are shown as transparent surfaces.
B. Immunoprecipitation of $GP_{\Delta Muc}$ and GP_{THL} by the indicated ant bodies. Samples were analyzed by immunoblot for GP1. *n*=3 replicates; representative image shown.
C. Class averages of single particles from negative-stain electron micrographs of Fab114 in complex with $GP_{\Delta Muc}$ and GP_{THL}.
D. Binding kinetics, as determined by biolayer interferometry, of $GP_{\Delta Muc}$ or GP_{THL} with Fab114, 13C6, or NPC1-dC at the indicated pH. K_Ds are plotted on a negative log scale. *No binding. *n*=2 replicates; representative experiment shown.
E. Inh bition of NPC1-dC binding to GP_{THL} by competitor proteins (NPC1-dC) or antibodies (mAb100, mAb114, 13C6, KZ52, or isotype control) was determined by biolayer interferometry. Dashed line represents 60% inhibition of binding. *n*=3 replicates; representative experiment shown.
Abbreviations: Fab114 and mAb114, ansuvimab-zykl

The authors noted that despite being in the same competition group as ansuvimab-zykl, the ZMapp mAb 13C6 failed to neutralize EBOV due to its inability to remain bound to GP after cathepsin cleavage. The authors and the Applicant emphasized that ansuvimab-zykl is novel in that it binds to the center of the GP1 chalice with a near-vertical angle of approach (85° with respect to the viral membrane) which allows access to the GP1 core.

Conclusions From Studies Supporting Mechanism of Action

- A summary of the data supporting the ansuvimab-zykl mechanism of action is provided in Table 68.
- Ansuvimab-zykl is a recombinant, fully human, IgG1κ mAb that targets the EBOV GP, preventing EBOV entry into cells.
- Ansuvimab-zykl was derived from a monoclonal antibody isolated from the peripheral blood mononuclear cells of a subject who both survived the 1995 Ebolavirus outbreak in Kikwit, DRC and maintained circulating antibody for more than 10 years after infection.
- The EBOV GP epitope targeted by ansuvimab-zykl is linear and comprised of GP amino acid residues 111-LEIKKPDGS-119.
- Ansuvimab-zykl binds EBOV GP without the mucin domain with a K_D of 0.2nM at pH 7.4 and 0.6nM at pH 5.3 as measured by biolayer interferometry.
- Ansuvimab-zykl blocks binding of EBOV GP1 to the Neiman Pick cell receptor 1 on host cells, inhibiting virus entry into the host cell.
- Binding of ansuvimab-zykl to GP blocks interaction between GP and NPC1.
- Ansuvimab-zykl exhibited Fc-mediated ADCC activity against cells expressing EBOV GP when effector cells were added.

Table 68. Summary of Ansuvimab-zykl Mechanism of Action Studies

mAb	Binds sGP	Binds GP	GP Binding (ELISA)	K_D (BLI)	Blocking	Epitope Type	Binding Region	Epitope
ansuvimab-zykl	Yes	Yes	0.02 µg/mL	0.2nM at pH 7.4 0.6nM at pH 5.3	Binding of ansuvimab-zykl to GP blocks interaction between GP and NPC1	Linear	Glycan cap and inner chalice of the EBOV GP1 subunit	111-119: LEIKKPDGS

Source: Review team analysis

18.1.2.2. Cell Culture Antiviral Activity Studies

Plaque Reduction Neutralization Test Assay

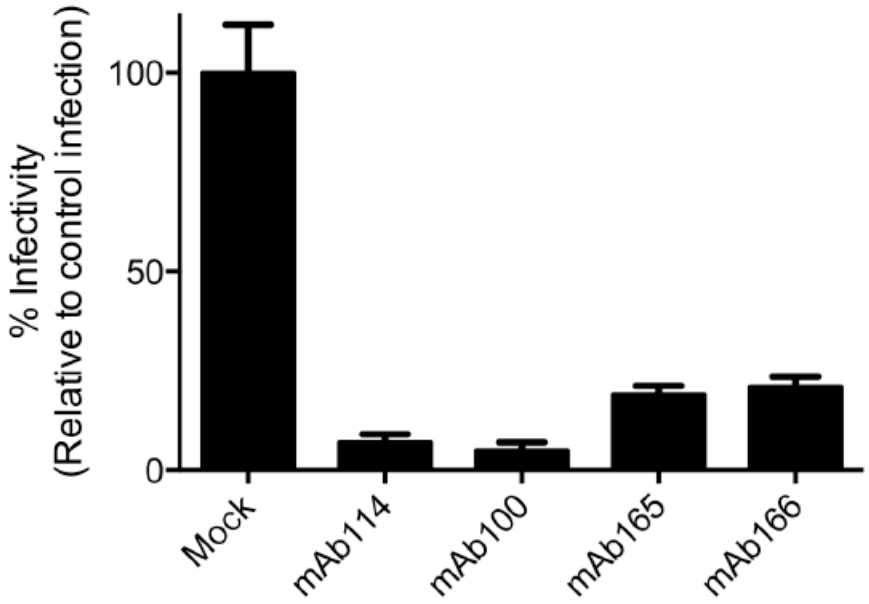
Ansuvimab-zykl was diluted in α-MEM (Gibco) and an equal volume of α-MEM containing 1,000 plaque forming units (PFU)/mL of the challenge virus was added to an equal volume of media containing ansuvimab-zykl to yield a concentration of 0.2 mg/mL of antibody and a target dose of 500 PFU/mL virus within the final neutralization mixture. A mock sample using media without an antibody added to an equal volume of challenge virus was used as a negative control. The mixtures were incubated together at 37°C for one hour and then 200 µL of the mixture was added to each well of a 6-well plate containing confluent Vero E6 cells for a target of 100 PFU/well. A plaque assay was then conducted as described previously (Shurtleff et al. 2012). After the incubation period, the monolayer was overlaid with 0.5% agarose in MEM. Plaques developed for one week and were stained with a neutral red overlay. The following day, plaques were counted, and neutralization was assessed by comparing plaque numbers in the mAb-treated versus mock-treated samples.

Neutralization of wild-type EBOV (Mayinga variant) was performed using the PRNT assay in Vero E6 cells (Figure 17). An EC_{50} value of 0.06 µg/mL was calculated from these data.

Pseudotyped Virus Neutralization Assay

Ansuvimab-zykl was assessed for neutralization activity using a single-round infection assay with EBOV (Mayinga variant) GP-pseudotyped lentivirus particles that express a luciferase reporter gene following entry (Sullivan et al. 2006). HEK293T cells were used as infection targets and incubated in a 96-well plate 1 day prior to infection with pseudovirus in the presence of serially diluted supernatant or ansuvimab-zykl. Infected target cells were lysed 72 hours after infection and assayed with the Luciferase Assay System or Bright Glo (Promega), using a Victor X3 Plate Reader (PerkinElmer) to detect luciferase activity.

Figure 17. Plaque Reduction Neutralization Assay Results



Source: Supplemental Figure S2 from (Corti et al. 2016)
Native EBOV (Mayinga variant) neutralization by the indicated mAbs at 0.2 µg/mL or media alone was performed under BSL-4 conditions using PRNT. Inhibition is calculated relative to virus incubated with media alone (Mock), mean ± SD. (n=1). mAb114 = ansuvimab-zykl.

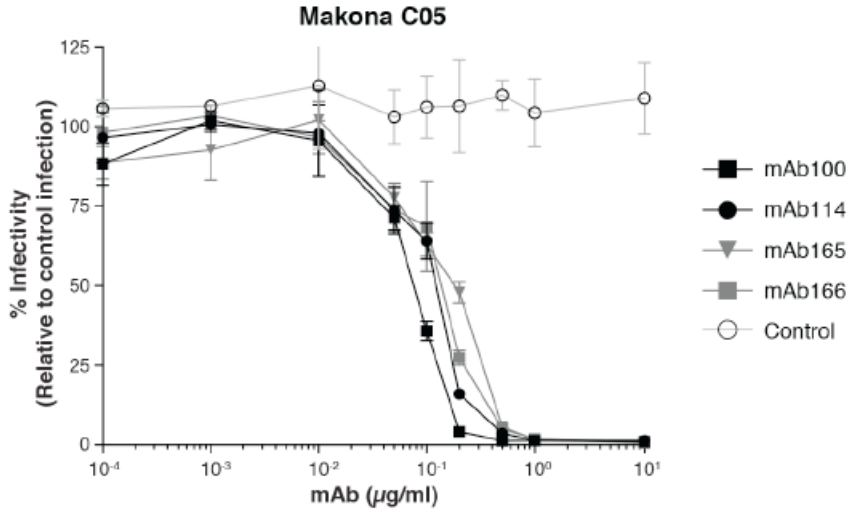
Ansuvimab-zykl neutralization occurred with an EC_{50} value of 0.09 µg/mL (Figure 18-A). Ansuvimab-zykl inhibited 100% of the virus, unlike KZ52, which consistently displayed only 80 to 90% maximum inhibition (Figure 18-B). The Applicant also reported that ansuvimab-zykl neutralized the 2014 West African EBOV Makona variant with an EC_{50} value of 0.15 µg/mL (Figure 17).

Figure 18. Pseudotype Virus Neutralization by Isolated Monoclonal Antibodies

A

mAb	IC50 (μg/mL)	95% CI	IC90 (μg/mL)	95% CI	IC99 (μg/mL)	95% CI	n
KZ52	0.06	0.02 to 0.14	17.21	8.47 to 35.00	>>1000	54,868	6
mAb 100	0.06	0.05 to 0.08	0.61	0.39 to 0.93	7.58	2.999 to 19.16	6
mAb 114	0.09	0.07 to 0.11	0.71	0.44 to 1.16	7.19	2.588 to 19.96	6
mAb 166	0.86	0.72 to 1.02	6.84	4.78 to 9.80	97.25	31.32 to 138.2	4
mAb 165	1.77	1.43 to 2.18	19.46	13.23 to 28.61	267.00	124.9 to 570.8	4

B



Source: Supplemental Figure S2 from (Corti et al. 2016)
A. Summary of pseudotyped lentivirus EBOV GP Mayinga variant virus neutralization assays were performed as in Figure 1B of source. EC_{50}, EC_{90}, and EC_{99} values were determined using nonlinear regression-variable slope (Graph Pad). 95% Confidence Interval (CI) and number of replicates (n) for each mAb.
B. Pseudotype EBOV Makona variant neutralization by mAb100 and mAb114. Lentivirus particles bearing GPs from EBOV Makona variant were incubated with serially diluted mAb100, mAb114, or isotype control. Infection measured as in Figure 13B, mean ± SD (n=1). mAb114 = ansuvimab-zykl.

The ADCC activity of ansuvimab-zykl was assessed in EBOV GP-transduced and nontransduced HEK293T target cells in the presence of antibody with effector cells added at an effector-to-target cell ratio of 1:50 and analyzed via flow cytometry. Ansuvimab-zykl mediated ADCC, with maximal activity observed at a mAb concentration of 0.03 μg/mL (Corti et al. 2016).

Antiviral Activity in Cell Culture in the Presence of Serum and Serum Proteins

No assessments were provided.

Cytotoxicity/Therapeutic Index

No assessments were provided; however, antibodies directed against viral proteins lacking homology to human proteins are typically not cytotoxic.

Combination Antiviral Activity in Cell Culture

No assessments were provided; however, no drugs were currently approved for the treatment of EBOV infection at the time this application was received by the FDA.

Resistance Development in Cell Culture

No assessments were provided. This will be the subject of a postmarketing requirement:

(1) **Resistance PMR #1:** Conduct a study to identify ansuvimab-zykl resistance pathways using a recombinant virus expressing EBOV GP to select and characterize several independent resistant isolates phenotypically and genotypically.

Conclusions From Studies Supporting Cell Culture Antiviral Activity

- Ansuvimab-zykl neutralized lentiviral particles pseudotyped with EBOV GP (Mayinga variant) in HEK293 cells with an EC_{50} value of 0.09 μg/mL.
- Ansuvimab-zykl neutralized lentiviral particles pseudotyped with EBOV GP (Makona variant) in HEK293 cells with an EC_{50} value of 0.15 μg/mL
- Ansuvimab-zykl neutralized wild-type EBOV (Mayinga variant) with an EC_{50} value of 0.06 μg/mL as determined by plaque reduction assay performed in Vero E6 cells.
- Ansuvimab-zykl mediated ADCC with maximal activity observed at a mAb concentration of 0.03 μg/mL.

Table 69. Summary of Cell Culture Data for Ansuvimab-zykl

	Live Virus PRA (EC_{50} Value) (μg/mL)			Pseudotype Virus (EC_{50} Value) (μg/mL)			ADCC Signaling HEK293/Tet-on/ EBOV GP	
Antibody	Kikwit	Makona	Mayinga	Kikwit	Makona	Mayinga	(μg/mL)	C1q Binding
ansuvimab-zykl	NA	NA	0.06	NA	0.15	0.09	0.03	No

Source: Review team's analysis
Abbreviations: NA, not assessed; PRA, plaque reduction assay

18.1.2.3. Pharmacokinetic Animal Studies

Study Title

Validation of "Quantitation of EBOV mAb114 in Rhesus Monkey Serum by ELISA"

Study Number

RB-NCR-004

Purpose

The objective of this study was to validate an ELISA for the quantitation of ansuvimab-zykl in rhesus monkey serum samples. The following parameters were evaluated during this validation: standard curve fit, intra- and inter-assay precision, sensitivity and ruggedness, selectivity, dilution linearity and hook effect, incurred sample re-analysis, stability of ansuvimab-zykl in rhesus monkey serum, and stability of the ansuvimab-zykl stock.

Conclusion

The validation of the method for the quantitation of ansuvimab-zykl in rhesus monkey serum samples by ELISA was conducted according to the validation study plan and amendment(s). Standard curve fit, and precision and accuracy met acceptance criteria. The ruggedness was not validated. Therefore, analyst B will perform all sample analysis activities associated with the current validation as the current validation was performed by one analyst (analyst B). Sensitivity of the assay is 0.390 µg/mL, which is the lower limit of quantitation, with a range of 0.390 to 10.000 µg/mL in rhesus monkey serum. The minimum required dilution was confirmed at 1/100. Samples can be diluted up to 1/480,000 dilution, i.e., 1/4,800 X 1/100 minimum required dilution. No hook effect was observed. Selectivity in rhesus monkey serum met acceptance criteria.

Stability of ansuvimab-zykl in rhesus monkey serum at 1.170 and 2,590.000 µg/mL was demonstrated for up to three freezing and thawing cycles at -60 to -80°C, storage at room temperature for up to 20 hours and 14 minutes (low level) and 20 hours and 12 minutes (high level), and long-term stability at -60 to -80°C for up to 16 weeks for both low and high levels. Stock stability of ansuvimab-zykl at 51.8 mg/mL was demonstrated for up to three freezing and thawing cycles at -60 to -80°C, storage at room temperature for up to 20 hours and 51 minutes, and storage at 2 to 8°C for up to 63 hours and 24 minutes. Incurred sample reanalysis met acceptance criteria. Overall, the method was found to be suitable for the quantitation of ansuvimab-zykl in rhesus monkey serum samples.

18.1.2.4. Antiviral Activity Animal Studies

Study Title

mAb114 Non-Human Primates Single Dose Studies Report

Study Number

RB-NCR-001 link to data

Protocol

No protocol number was provided. This study report provides details for three separate studies:

- **Study #1** – 50 mg/kg ansuvimab-zykl administered Day 1 postinfection
- **Study #2** – 50 mg/kg ansuvimab-zykl administered Day 5 postinfection
- **Study #3** – 30 mg/kg ansuvimab-zykl administered Day 5 postinfection

Purpose

Assess single doses of 50 mg/kg of ansuvimab-zykl with treatment starting on Day 1 and Day 5 and a single dose of 30 mg/kg of ansuvimab-zykl with treatment starting at Day 5 in NHPs challenged with EBOV

Institute That Conducted the Study

United States Army Medical Research Institute of Infectious Diseases (USAMRIID)

> ***Reviewer's Note:*** *The study reports from USAMRIID were not provided for any of these studies.*

Animals

All animals were Indian-origin rhesus macaques (Macaca mulatta), female, approximately 3 to 6 years of age, and were obtained from (b) (4)

Challenge Strain

Animals were transferred one week prior to challenge to the BSL-4 facility for exposure to a lethal (1,000 PFU) intramuscular (IM) injection of EBOV Kikwit variant challenge with challenge stock AIMS 22955/RIID R4368 (passage 4), which is 85% 8U genotype and contains a P430L polymorphism in the GP compared to "134" (GenBank #AY354458) (Kugelman et al. 2016). Of note, the T544I polymorphism associated with other challenge stocks was not detected in R4368 (passage 4) challenge stock. The same EBOV challenge strain was used for all three studies and was derived from a fatal human case of EBOV infection. The challenge stock was predominantly 8U at the time of challenge; however, the Applicant noted that data from a previous study indicates that the 7U:8U genotype ratio shifts over the first few days of in vivo EBOV infection, resulting in ~90% 7U genotype (Kugelman et al. 2015). The Applicant concluded that the major genotype of circulating virus would likely be 7U in the NHP study by Day 5 postinfection when ansuvimab-zykl treatment was initiated in two of the studies.

> ***Reviewer's note:*** *It is not clear if the 7U:8U genotype ratio shifts over the first few days of in vivo EBOV infection, resulting in ~90% 7U genotype are representative of a direct 7U challenge. Use of a predominantly 8U virus stock may effectively result in a delay of the disease course. Clinical Virology recommended that the Applicant assess the antiviral activity of ansuvimab-zykl in blinded NHP challenge study using a predominantly 7U challenge stock.*

Euthanasia Criteria

Primary Euthanasia Criteria

Primary euthanasia criteria assessments were performed daily, with 2 to 5 assessments performed during the critical disease phase (Days 7 to 11). Primary criteria scores were determined as follows:

0 = Alert, responsive, normal activity, free of disease signs or exhibits only resolved/resolving disease signs

1 = Slightly diminished general activity, subdued but responds normally to external stimuli

2 = Withdrawn, may have head down, fetal posture, hunched, reduced response to external stimuli

3 = Prostrate but able to rise if stimulated or moderate to dramatically reduced response to external stimuli

4 = Persistently prostrate, severely or completely unresponsive, may have signs of respiratory distress

These criteria enabled the study staff to euthanize 100% of the study population directly before the NHPs succumbed to Ebola virus disease.

Experimental Design

USAMRIID investigators were blinded to the investigational antibodies but not treatment status. Rhesus macaques were challenged with 1,000 PFU of EBOV Kikwit by IM injection and treated via IV injection in peripheral veins using ≤20-gauge butterfly needles over a period of 15 to 23 minutes in a single bolus via syringe pump starting on Day 1 or Day 5 postchallenge with 30 or 50 mg/kg of ansuvimab-zykl. Challenge studies included a single untreated animal (control). The Applicant provided the following rationale for using only one control animal: *the use of historical controls (n >25) allows for one untreated control to be used in each challenge experiment. Sample sizes of three animals per BioSafety Level-4 (BSL4) EBOV challenge group provide 80% power to detect a difference in survival rates assuming 100% survival (3/3 treated survive) versus 0% survival in negative controls at the 95% confidence level (1-tailed Fisher exact test).* While at USAMRIID, healthy monkeys were fed and checked daily. During the EBOV challenge study, blood was collected from the NHP for hematological, biochemical, and virologic analyses on Study Days 0, 3, 6, 8, 10, 14, 21, and 28. Prior to blood sampling or treatment, animals were anesthetized with ketamine or telazol. Following the development of clinical signs, animals were checked multiple times daily. Institute scoring criteria were used to determine timing of humane euthanasia under anesthesia.

Virologic Assessments

- **Mortality:** Mortality was assessed through the end of study at Day 28.
- **Quantitative RT-PCR (qRT-PCR) for circulating EBOV genomes:** EBOV viral load was determined by qRT-PCR assay using plasma from EBOV-exposed NHP. Samples were collected on Study Days 0, 3, 6, 8, 10, 14, 21, and 28.
- **Clinical signs:** Clinical signs were assessed but no data were provided in the study report.

Virology Assays

(1) **qRT-PCR:** EBOV viral load was determined by qRT-PCR assay using plasma from EBOV-exposed NHP. EDTA plasma was added to TriReagent LS (Sigma), 1 part to 3 parts, in preparation for qRT-PCR. Inactivated samples were extracted and eluted with AVE Buffer (QIAGEN, Valencia, CA) using a QIAamp Viral RNA Mini Kit (Qiagen, Valencia, CA). All samples were run on an Applied Biosystems 7500 Fast Dx Real-Time PCR instrument (Life Technologies, Grand Island, NY). Reactions were performed with SuperScript II One-Step RT-PCR System (Life Technologies, Grand Island, NY) with additional $MgSO_4$ added to a final concentration of 3.0mM. All samples were run in triplicate, 5 μL each. The average of the triplicates was multiplied by 200 to obtain genomes equivalents per mL, then multiplied by a dilution factor of 4 for the final

reported value. The sequences of the primers and probes for the EBOV glycoprotein were:

Forward Primer 5′ - TTT TCA ATC CTC AAC CGT AAG GC - 3′

Reverse Primer 5′ - CAG TCC GGT CCC AGA ATG TG - 3′

Probe 6FAM - CAT GTG CCG CCC CAT CGC TGC – TAMRA

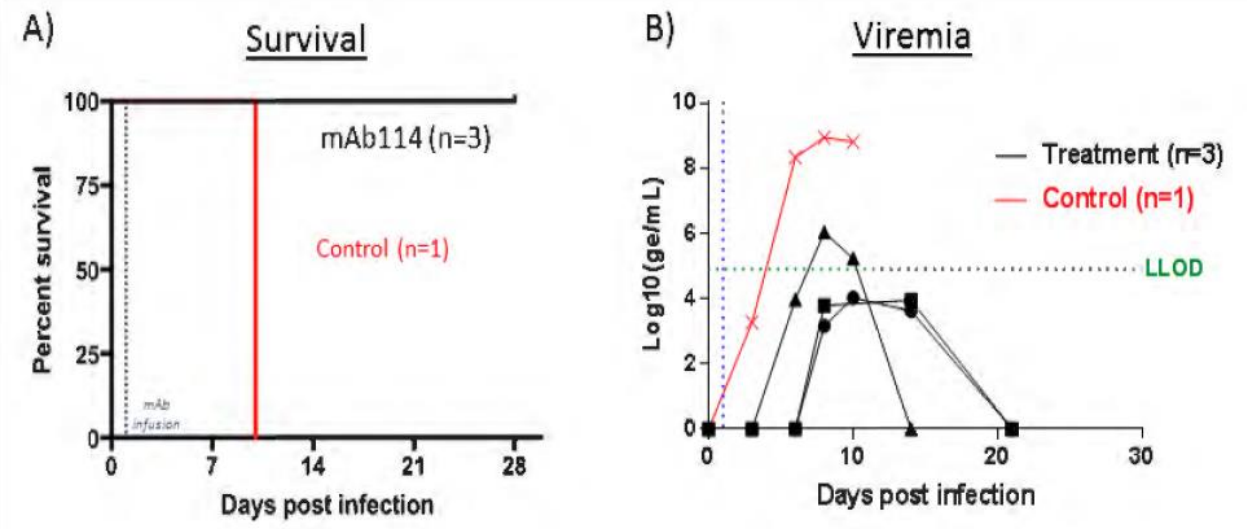
(1) The GE were determined using a synthetic RNA standard curve of known concentration.

Results

Study #1

A single dose of 50 mg/kg ansuvimab-zykl was administered 1-day postinfection. Four NHPs were challenged with EBOV Kikwit (8U) by IM injection on Day 0 and three NHPs were treated with ansuvimab-zykl on Day 1. All three of the NHPs that received ansuvimab-zykl on Day 1 survived the challenge, and the control animal was euthanized on Day 10 (Figure 19-A). In two of the three treated animals, viremia remained below levels of quantitation (<lower limit of quantification; 4.903 $\log_{10}$) of the RT-PCR assay; one animal had detectable viral RNA in plasma on Days 8 and 10 postchallenge. EBOV viral load was undetectable in all treated animals by Study Day 21 and remained undetectable through study end on Day 28 (Figure 19-B). The control animal was not able to clear or control viral infection and succumbed on Day 10 with a titer >1x10^8 GE/mL (Figure 19-B).

Figure 19. Survival and Reduced Viremia in NHPs Treated With 50 mg/kg of Ansuvimab-zykl 24 Hours After Challenge With EBOV Kikwit (8U)

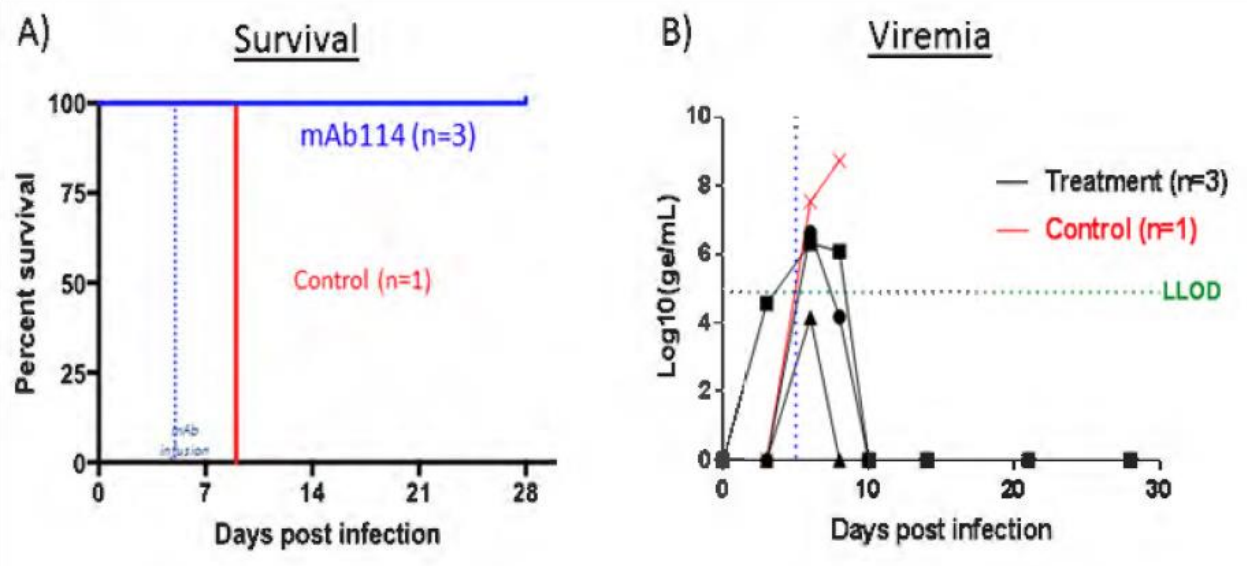


Source: Figure 1, page 6, RB-NCR-19-001 Study Report
A. Survival
B. Plasma viral load as determined by qRT-PCR
Abbreviations: mAb114, ansuvimab-zykl

Study #2

Rhesus macaques were challenged by IM injection with 1,000 PFU EBOV Kikwit (8U) on Day 0. On Day 5, three NHPs were treated with a single IV infusion of 50 mg/kg ansuvimab-zykl. The control animal received no treatment. All three animals that received ansuvimab-zykl treatment survived, and the control animal was euthanized on Day 9 (Figure 20-A). Viremia curves indicated detectable EBOV titers of up to $1x10^7$ GE/mL in plasma postchallenge with onset of viremia prior to ansuvimab-zykl treatment. EBOV viral load in all treated animals was undetectable by Study Day 10 and remained undetectable through study end on Day 28 (Figure 20-B). The control animal was not able to clear or control viral infection and succumbed to EBOV infection on Day 9 with a titer $>1x10^8$ GE/mL (Figure 20-B).

Figure 20. Survival and Reduced Viremia in NHPs Treated With 50 mg/kg of Ansuvimab-zykl 120 Hours After Challenge With EBOV Kikwit (8U)

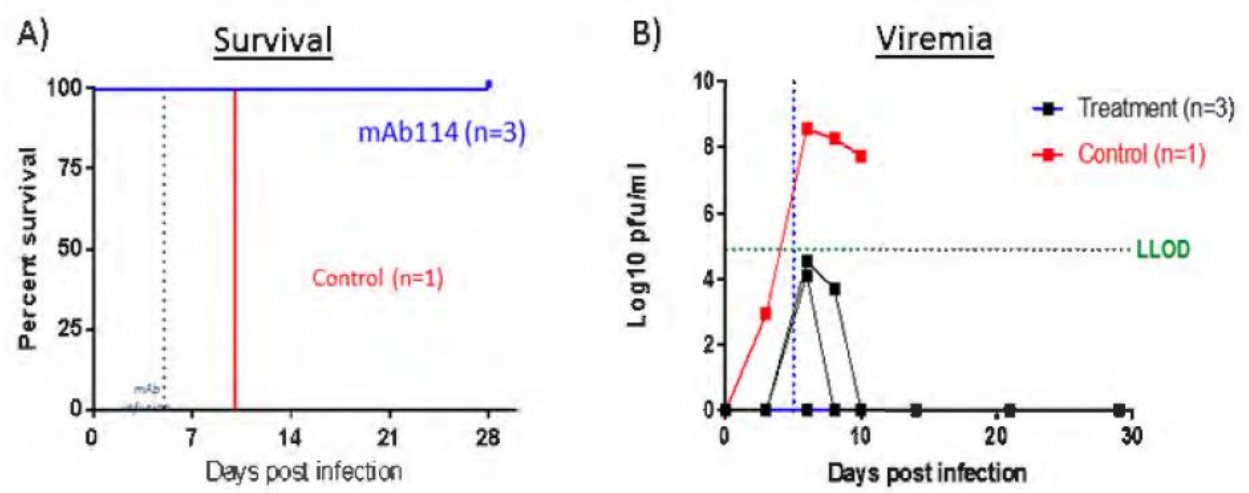


Source: Figure 2, page 7, RB-NCR-19-001 Study Report
A. Survival
B. Plasma viral load as determined by qRT-PCR.
Abbreviations: mAb114, ansuvimab-zykl

Study #3

Rhesus macaques were challenged with EBOV Kikwit (8U) at 1,000 PFU IM injection on Day 0. On Day 5, three NHPs were treated with a single IV infusion of 30 mg/kg ansuvimab-zykl. The control animal received no treatment. All three animals that received ansuvimab-zykl treatment survived. The control animal died on Day 10 (unknown if euthanasia was used) (Figure 21-A). Viremia curves demonstrated up to 4.5 $\log_{10}$ of detectable virus in the plasma postchallenge with onset of viremia prior to ansuvimab-zykl treatment. The EBOV viral load in all treated animals was undetectable by Study Day 10 and remained undetectable through study end on Day 28 (Figure 21-B). The control animal was not able to clear or control viral infection and succumbed on Day 10 with a titer $>1x10^8$ GE/mL.

Figure 21. Survival and Reduced Viremia in NHPs Treated With 30 mg/kg of Ansuvimab-zykl 120 Hours After Challenge With EBOV Kikwit (8U)



Source: Figure 1, page 6, RB-NCR-19-001 Study Report
A. Survival
B. Plasma viral load as determined by qRT-PCR
Abbreviations: mAb114, ansuvimab-zykl.

Overall, the results of the single-dose studies described herein show that 100% of NHPs treated with a single 50 mg/kg dose of ansuvimab-zykl on Day 1 or Day 5 postinfection survived and were protected from EBOV. A follow-up study evaluating a single 30 mg/kg dose of ansuvimab-zykl administered at Day 5 postinfection also showed protection in 3/3 NHP from EBOV death. In contrast, untreated NHPs succumbed to disease in 9 to 10 days following infection.

Conclusion

The results of these studies demonstrate that ansuvimab-zykl can protect rhesus macaques from EBOV infection even when initiation of treatment is delayed for five days. When administered as a single 50 mg/kg or 30 mg/kg dose up to five days postinfection, ansuvimab-zykl reduced EBOV viremia and protected animals from death. Viral load in the plasma also decreased to undetectable levels within 5 days following ansuvimab-zykl treatment, with no transient or rebound viremia.

Study Title

mAb114 Non-Human Primates Dose-Down Study Report

Study Number

RB-NCR-002 link to data

Protocol

No protocol number was provided. This study report provides details for two separate studies:

- **Study #1** – 50, 15, or 5 mg/kg ansuvimab-zykl administered on Days 1, 2, or 3 postinfection
- **Study #2** – 5, 2, or 1 mg/kg ansuvimab-zykl administered on Days 1, 2, or 3 postinfection

Purpose

To test the therapeutic potential of ansuvimab-zykl in the lethal EBOV rhesus macaque challenge model at doses lower than 50 mg/kg.

Institute That Conducted the Study

United States Army Medical Research Institute of Infectious Diseases

Animals

All animals were Indian-origin rhesus macaques (Macaca mulatta), female, approximately 3 to 6 years of age, and were obtained from (b) (4) Animals were randomly assigned to treatment groups based on sequential selection from a population inventory.

Challenge Strain

Animals were transferred one week prior to challenge to the BSL-4 facility for exposure to a lethal (1,000 PFU) IM injection of EBOV Kikwit variant challenge with challenge stock AIMS 22955/RIID R4368 (passage 4), which is 85% 8U genotype and contains a P430L polymorphism in the GP compared to "134" (GenBank #AY354458) (Kugelman et al. 2016). Of note, the T544I polymorphism associated with other challenge stocks was not detected in R4368 (passage 4) challenge stock. The same EBOV challenge strain was used in both studies described in this report and it was originally derived from a fatal human case of EBOV infection. The challenge stock was predominantly 8U (85%) at the time of challenge; however, the Applicant noted that data from a previous study indicates that the 7U:8U genotype ratio shifts over the first few days of in vivo EBOV infection, resulting in ~90% 7U genotype (Kugelman et al. 2015). The Applicant concluded that the major genotype of circulating virus would likely be 7U in the NHP study by Day 5 postinfection; however, treatment in these studies started 1-day after challenge.

> ***Reviewer's note:*** *It is not clear if the 7U:8U genotype ratio shifts over the first few days of in vivo EBOV infection, resulting in ~90% 7U genotype are representative of a direct 7U challenge. Use of a predominantly 8U virus stock may effectively result in a delay of the disease course. Clinical Virology recommended that the Applicant assess the antiviral activity of ansuvimab-zykl in blinded NHP challenge study using a predominantly 7U challenge stock.*

Euthanasia Criteria

Primary Euthanasia Criteria

Primary euthanasia criteria assessments were performed daily, with 2 to 5 assessments performed during the critical disease phase (Days 7 to 11). Primary criteria scores were determined as follows:

> 0 = alert, responsive, normal activity, free of disease signs or exhibits only resolved/resolving disease signs
>
> 1 = slightly diminished general activity, subdued but responds normally to external stimuli

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3 = prostrate but able to rise if stimulated or moderate to dramatically reduced response to external stimuli

4 = persistently prostrate, severely or completely unresponsive, may have signs of respiratory distress

These criteria enabled the study staff to euthanize 100% of the study population directly before the NHPs succumbed to Ebola virus disease.

Experimental Design

USAMRIID investigators were blinded to investigational antibodies but not treatment status. Rhesus macaques were challenged with 1,000 PFU of EBOV Kikwit (8U) by IM injection and treated via IV injection in peripheral veins using ≤20-gauge butterfly needles over a period of 15 to 23 minutes in a single bolus via syringe pump on Days 1, 2, and 3 postchallenge with doses of 1, 2, 5, 15, or 50 mg/kg of ansuvimab-zykl. Challenge studies included a single untreated animal (control). The Applicant provided the following rationale for using only one control animal: *the use of historical controls (n >25) allows for one untreated control to be used in each challenge experiment. Sample sizes of three animals per BioSafety Level-4 (BSL4) EBOV challenge group provide 80% power to detect a difference in survival rates assuming 100% survival (3/3 treated survive) versus 0% survival in negative controls at the 95% confidence level (1-tailed Fisher exact test).* While at USAMRIID, healthy monkeys were fed and checked daily. During the EBOV challenge study, blood was collected from the NHP for hematological, biochemical, and virologic analyses on Study Days 0, 3, 6, 8, 10, 14, 21, and 28. Prior to blood sampling or treatment, animals were anesthetized with ketamine or telazol. Following the development of clinical signs, animals were checked multiple times daily. Institute scoring criteria were used to determine timing of humane euthanasia under anesthesia.

Virologic Assessments

- **Mortality:** Mortality was assessed through the end of study at Day 28.
- **qRT-PCR for circulating EBOV genomes:** EBOV viral load was determined by qRT-PCR assay using plasma from EBOV-exposed NHP. Samples were collected on Study Days 0, 3, 6, 8, 10, 14, 21, and 28.
- **Clinical signs:** Clinical signs were assessed but no data were provided in the study report.

Virology Assays

(1) **qRT-PCR:** EBOV viral load was determined by qRT-PCR assay using plasma from EBOV-exposed NHP. EDTA plasma was added to TriReagent LS (Sigma), 1 part to 3 parts, in preparation for qRT-PCR. Inactivated samples were extracted and eluted with AVE Buffer (QIAGEN, Valencia, CA) using a QIAamp Viral RNA Mini Kit (Qiagen, Valencia, CA). All samples were run on an Applied Biosystems 7500 Fast Dx Real-Time PCR instrument (Life Technologies, Grand Island, NY). Reactions were performed with SuperScript II One-Step RT-PCR System (Life Technologies, Grand Island, NY) with

additional $MgSO_4$ added to a final concentration of 3.0mM. All samples were run in triplicate 5 µL each. The average of the triplicates was multiplied by 200 to obtain genomes equivalents per mL, then multiplied by a dilution factor of 4 for the final reported value. The sequences of the primers and probes for the EBOV glycoprotein were:

Forward Primer 5′ - TTT TCA ATC CTC AAC CGT AAG GC - 3′

Reverse Primer 5′ - CAG TCC GGT CCC AGA ATG TG - 3′

Probe 6FAM - CAT GTG CCG CCC CAT CGC TGC – TAMRA

The GE were determined using a synthetic RNA standard curve of known concentration.

(2) **Clinical chemistry:** Platelet and lymphocyte counts were determined from blood samples collected in tubes containing EDTA using a laser-based hematologic Hemavet or Analyzer (Coulter Electronics).

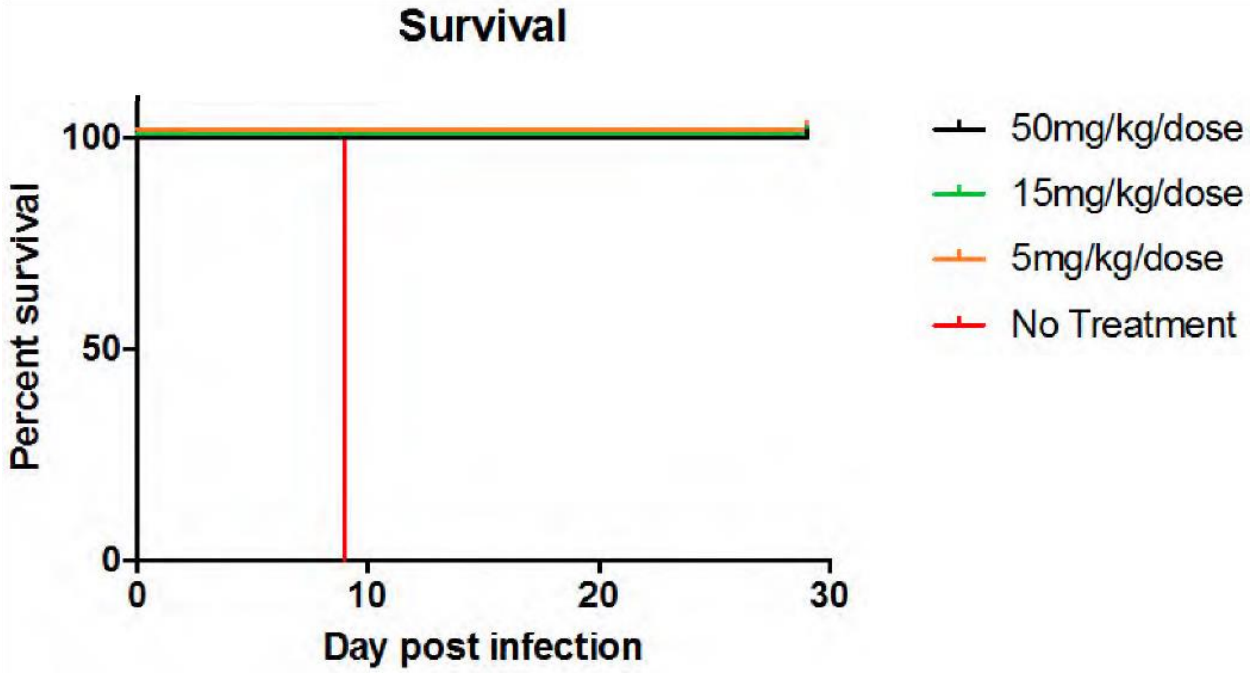
(3) **Serum concentration of ansuvimab-zykl:** Anti-EBOV GP IgG ELISA titers were measured as described previously (Geisbert et al. 2011). ELISA titers are expressed as EC_{90}, reciprocal serum dilution values, which represent the dilution at which there is a 90% decrease in antigen binding.

Results

Study #1

Ten rhesus macaques were challenged by IM injection with EBOV Kikwit (8U) at 1,000 PFU on Day 0. On Days 1, 2, and 3, three NHPs per treatment group received an IV infusion of 50, 15, or 5 mg/kg ansuvimab-zykl. The control animal received no treatment. All three groups of animals treated with ansuvimab-zykl survived, with low dose protection observed at 5 mg/kg. The untreated control animal was euthanized on Day 9 (Figure 22).

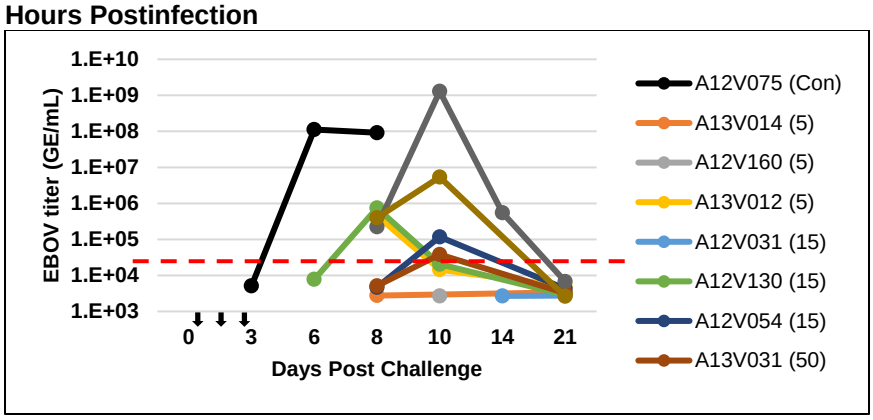
Figure 22. Survival of Rhesus Macaques Challenged With EBOV Kikwit Following Treatment With a Three-Dose, Daily Regimen of Ansuvimab-zykl at 50, 15, or 5 mg/kg Initiated 24 Hours Postinfection



Source: Figure 1, page 7, Study Report RB-NCR-19-002

Viral load data were provided as an addendum to the study report and an analysis was performed. The only quantifiable viral titer detected prior to or occurring on Day 6 was in the control animal, which had a plasma titer of $1x10^8$ GE/mL on Day 6 (Figure 23), which was maintained until Day 8, just prior to euthanization on Day 9. One NHP in the 15 mg/kg treatment group had an increase in plasma titer of 2 $\log_{10}$ between Days 6 and 8, and two NHPs, both in the 50 mg/kg treatment group, had increases in plasma viral load in the quantifiable range of the assay ranging between 1.25 and 4 $\log_{10}$ GE/mL between Days 8 and 10 (Figure 23). These results indicate that resistance may have developed in several of the NHPs prior to the adaptive immune response of the NHPs, which likely cleared the remaining virus after Day 8. No resistance data were provided for this study.

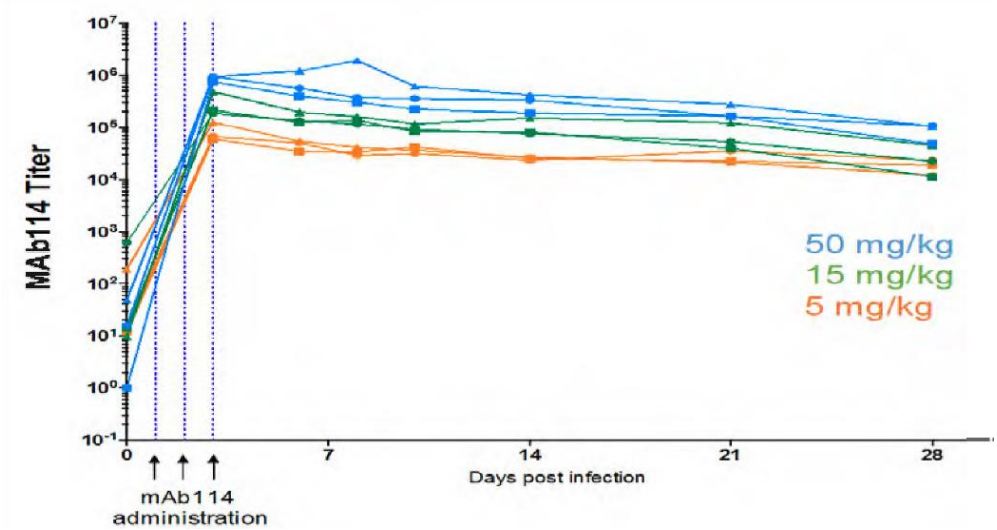
Figure 23. EBOV Titer Among Rhesus Macaques Challenged With EBOV Kikwit Following Treatment With a Three-Dose, Daily Regimen of Ansuvimab-zykl at 50, 15, or 5 mg/kg Initiated 24 Hours Postinfection



Source: DAV analysis with data from Study Report RB-NCR-19-002)
Red dashed line: LLOQ of assay

Additionally, ansuvimab-zykl was demonstrated to be present in the serum of all treated animals in a dose-dependent manner (Figure 24).

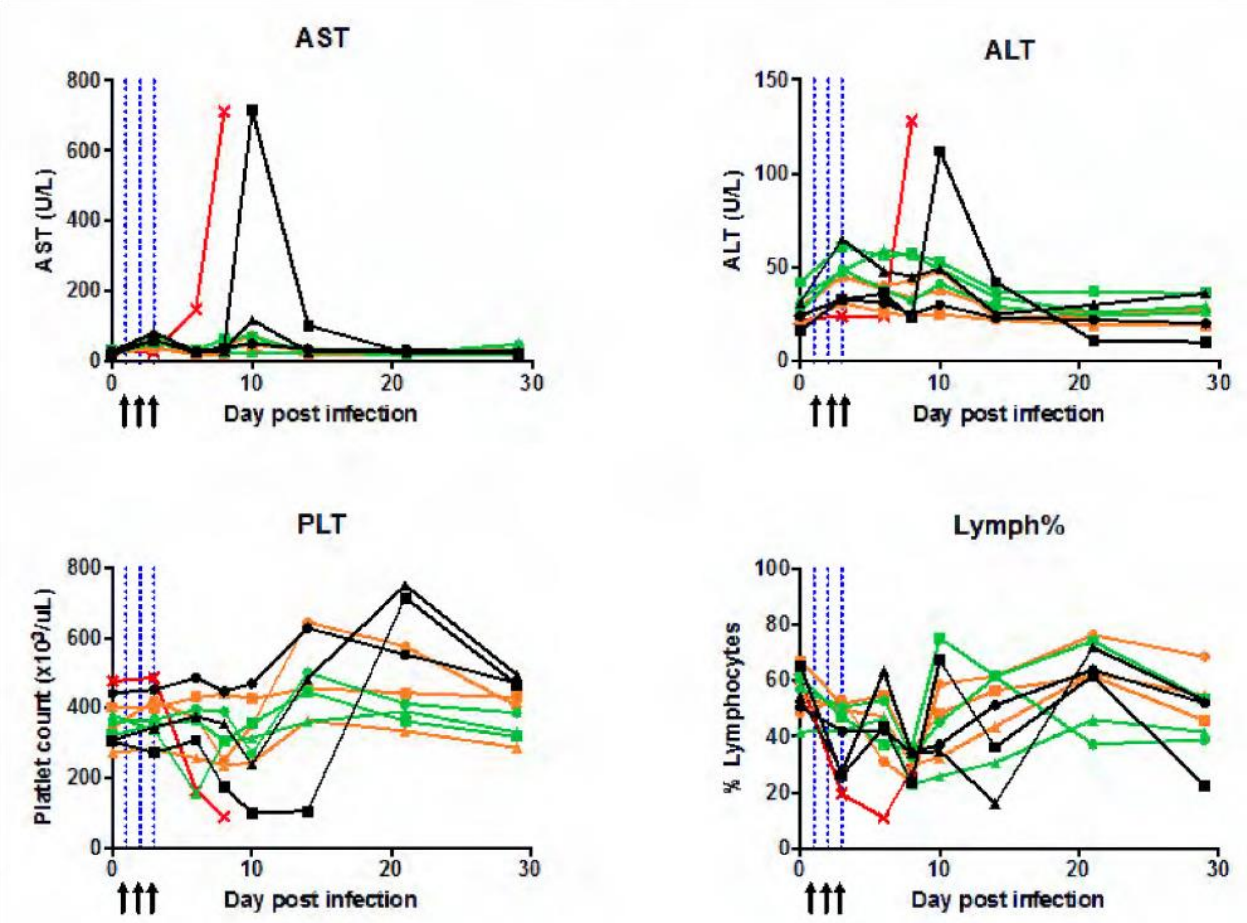
Figure 24. Serum Concentration of Ansuvimab-zykl in Rhesus Macaques Following EBOV Challenge and Treatment With a Three-Dose, Daily Regimen of Ansuvimab-zykl at 50, 15, or 5 mg/kg Initiated 24 Hours Postinfection



Source: Figure 2, page 7, Study Report RB-NCR-19-002

Clinical parameters commonly monitored in NHP ebolavirus challenge studies (ALT, AST, platelets, and lymphocytes) reflected changes consistent with both challenge and successful treatment of infection (Figure 25).

Figure 25. Selected Chemistry Data in Rhesus Macaques Following EBOV Challenge and Treatment With a Three-Dose, Daily Regimen of Ansuvimab-zykl at 50, 15, or 5 mg/kg Initiated 24 Hours Postinfection

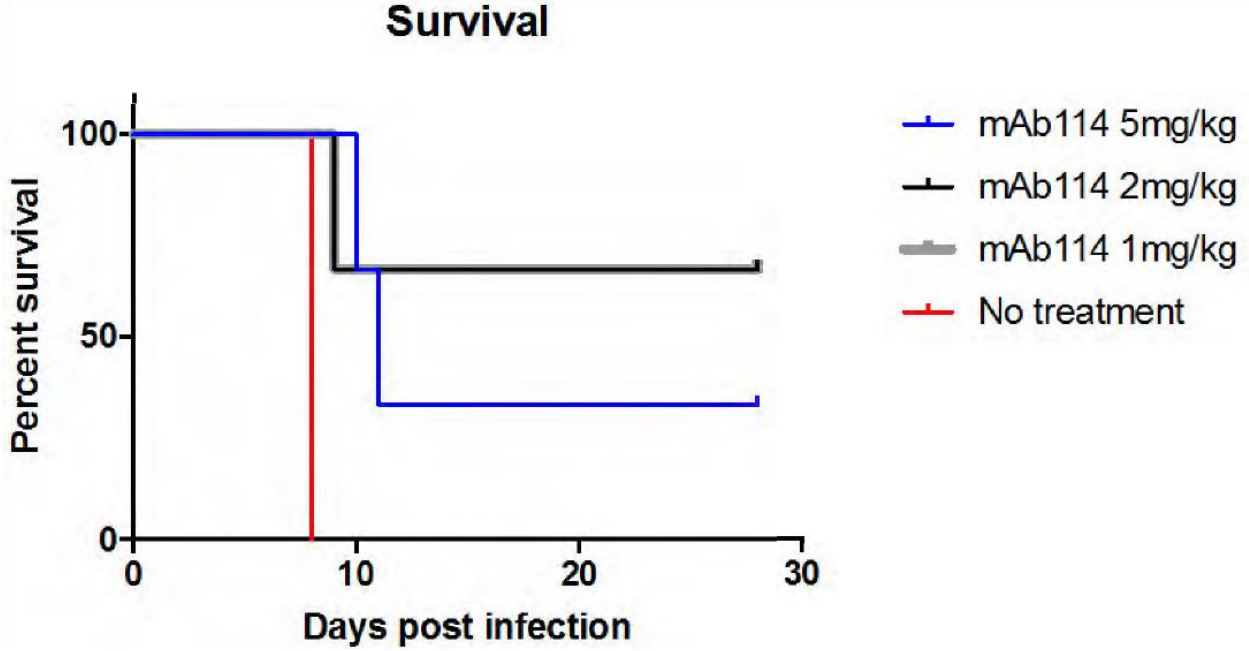


Source: Figure 3, page 8, Study Report RB-NCR-19-002
Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet

Study #2

Ten rhesus macaques were challenged by IM injection with EBOV Kikwit (8U) at 1,000 PFU on Day 0. On Days 1, 2, and 3, three NHPs per treatment group received an IV infusion of 5, 2, or 1 mg/kg ansuvimab-zykl. The control animal received no treatment. In this experiment, reduced protection from lethal infection was observed in the lower dose treatment groups in this study compared to previous studies using higher doses of ansuvimab-zykl. Of note, only 1/3 (33%) of NHPs in the 5 mg/kg treatment group survived lethal challenge in contrast to the results observed in Study 1 where 3/3 (100%) of NHPs in the 5 mg/kg treatment group survived challenge. In the 2 and 1 mg/kg treatment groups, 2/3 (67%) of NHPs survived lethal challenge (Figure 26). The Applicant stated that virologic breakthrough was observed at all three doses, including 5 mg/kg that was previously fully protective, indicating that breakthrough is likely to occur at or just below 5 mg/kg in NHPs in this model. However, no viral load data were summarized in the report or provided in the addendum. The untreated control animal died on Day 8 as expected but was not reported if the NHP was euthanized or found dead in cage.

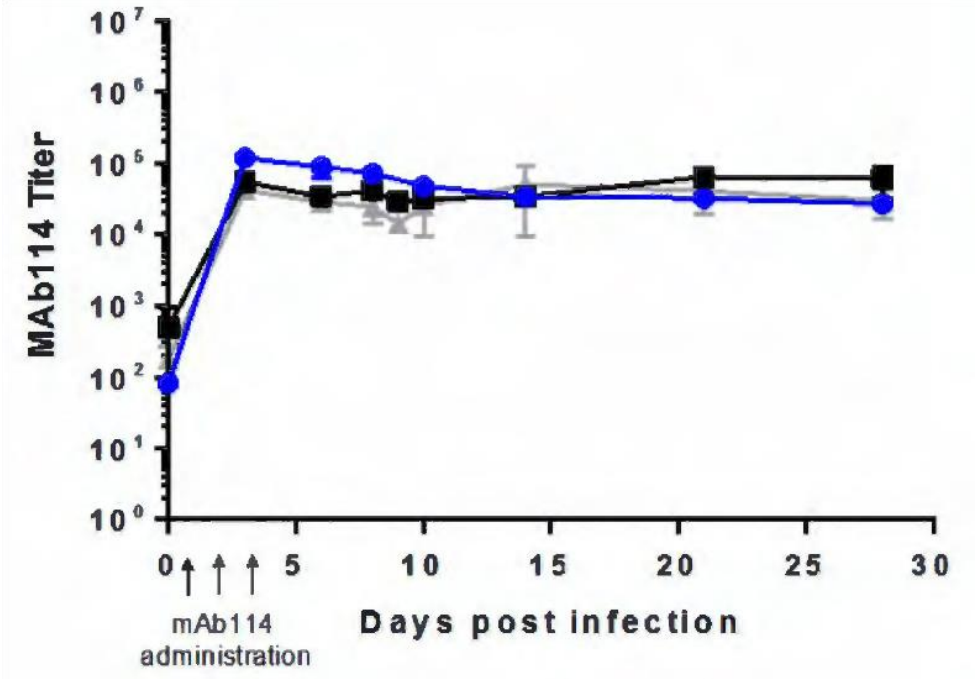
Figure 26. Survival of Rhesus Macaques From EBOV Challenge Following Treatment With a Three-Dose, Daily Regimen of Ansuvimab-zykl at 5, 2, or 1 mg/kg Initiated 24 Hours Postinfection



Source: Figure 4, page 9, Study Report RB-NCR-19-002

Serum ansuvimab-zykl was demonstrated to be present in all treated animals (Figure 27).

Figure 27. Serum Concentration of Ansuvimab-zykl in Rhesus Macaques Following EBOV Challenge and Treatment With a Three-Dose, Daily Regimen of Ansuvimab-zykl at 5, 2, or 1 mg/kg Initiated 24 Hours Postinfection



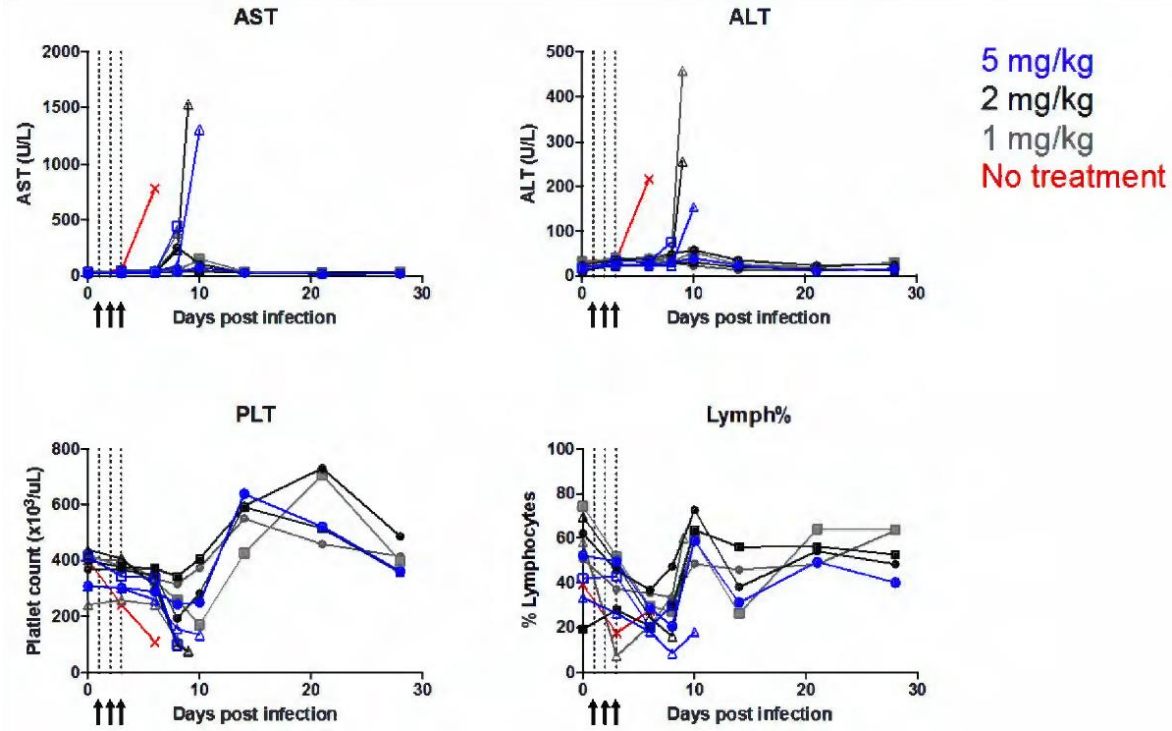
Source: Figure 5, page 10, Study Report RB-NCR-19-002

As in Study #1, clinical parameters commonly monitored in NHP ebolavirus challenge studies (ALT, AST, platelets, and lymphocytes) reflected changes consistent with partially treated infection (Figure 28).

Conclusion

The results of these studies demonstrate that ansuvimab-zykl administered as a three-dose, daily regimen can protect rhesus macaques from *Zaire ebolavirus* infection at doses lower than 50 mg/kg. Protection from EBOV challenge was maintained using the 3-dose, 15 mg/kg regimen, and doses of ≤5 mg/kg IV given on days 1, 2, and 3 appear to partially treat NHPs in this challenge model. The data in this high challenge dose, accelerated disease model indicate there is a threshold level of ansuvimab-zykl in serum or tissues below which therapeutic efficacy is reduced. Importantly, the animals treated with partially protective doses had similar, or delayed, time-to-death as compared to the control animal and historical controls indicating no evidence of enhanced illness.

Figure 28. Selected Chemistry Data in Rhesus Macaques Following EBOV Challenge and Treatment With a Three-Dose, Daily Regimen of Ansuvimab-zykl at 5, 2, or 1 mg/kg Initiated 24 Hours Postinfection



Source: Figure 6, page 10, Study Report RB-NCR-19-002

Conclusions From Studies Performed in Nonhuman Primates

Challenge experiments in rhesus macaques were performed with 1,000 PFU IM injection with EBOV Kikwit variant. Of note, USAMRIID investigators were blinded to the investigational antibodies but not treatment status. The challenge stock (AIMS 22955/RIID R4368; passage 4) contained a P430L polymorphism in the GP compared to Kikwit 1995 strain“134” (GenBank #AY354458) (Kugelman et al. 2016); however, the T544I polymorphism associated with other challenge stocks was not detected in the R4368 (passage 4) challenge stock. Of note, the R4368

(passage 4) challenge stock was predominantly 8U (85%) at the time of challenge; however, the Applicant noted that data from a previous study indicate that the 7U:8U genotype ratio shifts over the first few days of in vivo EBOV infection, resulting in ~90% 7U genotype (Kugelman et al. 2015). The Applicant concluded that the major genotype of circulating virus would likely be 7U in the NHP study by Day 5 postinfection when ansuvimab-zykl treatment was initiated in two of the studies. It is not clear if the 7U:8U genotype ratio shifts over the first few days of in vivo EBOV infection, resulting in ~90% 7U genotype are representative of a direct 7U challenge. Use of a predominantly 8U virus stock may effectively result in a delay of the disease course. Clinical Virology recommended that the Applicant assess the antiviral activity of ansuvimab-zykl in blinded NHP challenge study using a predominantly 7U challenge stock.

The highest dose assessed in NHPs was 50 mg/kg ansuvimab-zykl administered as a single dose 1 (n=3) or 5 (n=3) days after challenge or three doses (n=3) administered 1, 2, and 3 days after challenge. All nine of the NHPs that received the 50 mg/kg dose at the various dosing days survived the EBOV Kikwit challenge and none of the control animals survived (mean time-to-death =9.33 days). Lower doses were also assessed. All three NHPs treated with a dose of 30 mg/kg ansuvimab-zykl administered as a single dose 5 days (n=3) after challenge survived the EBOV Kikwit challenge whereas the control animal was euthanized 10 days after infection.

A dose-down study was performed to assess three lower doses, including 1 (n=3), 2(n=3), 5 (n=3), or 15 (n=3) mg/kg of ansuvimab-zykl administered 1, 2, and 3 days after challenge. For all dose groups, two-thirds of the animals survived the EBOV Kikwit challenge whereas the control animals (n=2) were euthanized 8 and 9 days after challenge. Of note, the 5 mg/kg dose administered 1, 2, and 3 days after challenge was assessed in two independent studies with three NHPs in each but had variable results with 3/3 NHPs surviving the EBOV Kikwit challenge in one group but only 1/3 NHPs surviving challenge in the second group (Table 70).

Table 70. Summary of Nonhuman Primate (NHP) Challenge Studies Performed With Ansuvimab-zykl

Study	Substudy	Group	Days After Challenge	Size (n)	Treatment	Dose (mg/kg)	NHP	Death (Day)	EBOV Titer GE/mL (Day)	Survivors (%)	MTD in Days (n)
RB-NCR-001	Study 1	Control	NA	1	None	0	14089	10	Und (1)	0/1 (0)	10 (1)
		ansuvimab-zykl, 50 mg	1	3	ansuvimab-zykl	50	13175	28	Und (1)	3/3 (100)	28 (3)
							14031	28	Und (1)		
							14059	28	Und (1)		
	Study 2	Control	NA	1	None	0	14151	9	Und (1)	0/1 (0)	9 (1)
		ansuvimab-zykl, 50 mg	5	3	ansuvimab-zykl	50	14117	28	Und (3)	3/3 (100)	28 (3)
							14081	28	36,900 (3)		
							13207	28	Und (3)		
	Study 3	Control	NA	1	None	0	NP	10	NP	0/1 (0)	10 (1)
		ansuvimab-zykl, 30 mg	5	3	ansuvimab-zykl	30	NP	28	NP	3/3 (100)	28 (3)
							NP	28	NP		
							NP	28	NP		
RB-NCR-002	Study 1	Control	NA	1	None	0	A12V075	9	Und (1)	0/1 (0)	9 (1)
		ansuvimab-zykl, 50 mg	Days 1, 2, and 3	3	ansuvimab-zykl	50	A13V031	28	Und (1)	3/3 (100)	28 (3)
							A12V113	28	Und (1)		
							A12V112	28	Und (1)		
		ansuvimab-zykl, 15 mg	Days 1, 2, and 3	3	ansuvimab-zykl	15	A12V054	28	Und (1)	3/3 (100)	28 (3)
							A12V130	28	Und (1)		
							A12V031	28	Und (1)		
		ansuvimab-zykl, 5 mg	Days 1, 2, and 3	3	ansuvimab-zykl	5	A13V012	28	Und (1)	3/3 (100)	28 (3)
							A12V160	28	Und (1)		
							A13V014	28	Und (1)		
	Study 2	Control	NA	1	None	0	NP	8	NP	0/1 (0)	8 (1)

Study	Substudy	Group	Days After Challenge	Size (n)	Treatment	Dose (mg/kg)	NHP	Death (Day)	EBOV Titer GE/mL (Day)	Survivors (%)	MTD in Days (n)
		ansuvimab-zykl, 5 mg	Days 1, 2, and 3	3	ansuvimab-zykl	5	NP NP NP	NP NP NP	NP NP NP	1/3 (33)	10.5 (2)
		ansuvimab-zykl, 2 mg	Days 1, 2, and 3	3	ansuvimab-zykl	2	NP NP NP	NP NP NP	NP NP NP	2/3 (67)	9 (1)
		ansuvimab-zykl, 1 mg	Days 1, 2, and 3	3	ansuvimab-zykl	1	NP NP NP	NP NP NP	NP NP NP	2/3 (67)	9 (1)

Source: Review team analysis
Abbreviations: EBOV, *Zaire ebolavirus;* GE, genome equivalents; MTD, mean time to death; NA, not applicable; NP, not provided; Und, undetermined

18.1.2.5. Resistance Studies

Study Title

Report on Ituri virus variants

Study Number

RIVV-Report

Purpose

The purpose of this study was to identify potential resistance-associated substitutions that were detected in EBOV GP sequences derived from samples collected from patients who were associated with the EBOV outbreak in the North Kivu province of the DRC, which had infected over 3000 people since it was first identified in August of 2018.

Methods

In collaboration with the University of Nebraska Medical Center (UNMC), the INRB obtained over 569 virus genome sequences from subjects of epidemiologic interest during the Ebola virus disease outbreak in the North Kivu province of the DRC. These sequences are available to the public via Nextstrain. The VRC, in collaboration with the INRB, has been working to determine virologic consequences of the evolving GP gene.

As part of this collaboration, multiple virus GP gene variants were created based upon the genomic sequences obtained during the outbreak thus far, (Table 71) for systematic evaluation of the GP structure and function. When compared to the original 1976 EBOV Mayinga variant, the initial virus consensus sequence from patients in Mandima, Ituri Province contained 12 changes in GP residues (Table 71). None of these changes occurred in the primary epitope targeted by ansuvimab-zykl, which has been identified and published as amino acid residues 111-119, LEIKKPDGS (Misasi et al. 2016).

Table 71. Initial Ituri Variant (18FHV089) Changes Relative to Mayinga (1976)

Item #	INRB/UNMC Seq. ID	Sample Date	GP Variations Relative to Mayinga
1	18FHV089	7/27/2018	V3A/V310A/L368P/S377P/S422P/P429T/A432T/T435A/F443L/ E458K/K478R/I544T

Source: Table 1, page 3, RIVV Study Report

Of the 569 virus genomic sequences that were obtained by the INRB and UNMC efforts since the start of the outbreak, there were 50 positions in subsequent isolates that had amino acid changes (relative to the initial EBOV Ituri variant), representing an additional 49 unique EBOV Ituri GP variants. One of these substitutions, GP_L111I, occurred at a position that is part of the ansuvimab-zykl epitope (Table 72). An independent search of sequences in public databases also identified a GP_L111F substitution that arose during the 2014-2015 EBOV Makona outbreak in West Africa (accession number AKI84062.1; (Carroll et al. 2015)). Phenotypic assessment of these substitutions will be addressed in postmarketing actions.

Table 72. List of Amino Acid Substitutions in EBOV GP Found in North Kivu Provence

Pos	Sub	Pos	Sub	Pos	Sub	Pos	Sub
I6	M	S210	P	S363	P	S456	I
F19	L	G212	D	P377	L	T464	N
F31	S	Y213	H	K381	Q	T469	A
V48	I	S246	A	P382	L	I482	T
G67	R	T429	A	S387	N	I504	F
V75	A	E258	K	T391	A	G546	R
T83	A	I260	M	K395	Q	G557	R
V96	M	N268	D	P421	S	I584	V
L111	**I**	G271	E	P422	L	I610	V
G128	W	E280	G	T429	A	P612	L
R130	Q	N313	D	K439	R	D640	N
A189	G	I318	V	T448	S		
P209	L	V351	A	N454	S		

Source: Appendix A, page 12, RIVV Study Report
Highlighted substitution occurred at a position that is part of the ansuvimab-zykl epitope.
Abbreviations: EBOV, *Zaire ebolavirus*; GP, glycoprotein; Pos, EBOV GP amino acid position; sub, substitution

The changes in EBOV Ituri and its related variants were found throughout both GP subunits (i.e., GP1 and GP2) and in most cases, their impact on virologic function had not been investigated. Therefore, preliminary studies in this report were aimed at assessing structural consequences and effects on steps in virus entry during GP evolution across and within outbreaks.

Of note, 12 substitutions were detected in the EBOV sequences from two or more subjects, but none of these positions were proximal to the ansuvimab-zykl epitope, and the Applicant reported that none of these substitutions were within 10 Angstroms of the residues that comprise the ansuvimab-zykl epitope (Table 73). Of note, the treatment status of the subjects from whom sequences were derived was unknown.

Table 73. Amino Acid Substitutions in EBOV GP Found in North Kivu Provence That Occurred in Two or More Patient Samples

GP POS	6	19	31	75	210	258	271	280	377	391	429	469
Wt AA	I	F	F	V	S	E	G	E	P	T	T	T
SUB	M	L	S	A	P	K	E	G	L	A	A	A

Source: Appendix A, page 12, RIVV Study Report
Abbreviations: EBOV, *Zaire ebolavirus*; GP, glycoprotein; GP POS, EBOV GP amino acid position; SUB, substitution; Wt AA, wild type amino acid

Results

The INRB and UNMC analysis found that the majority of the EBOV GP amino acid variants were found only one time, with ten sequences having occurrences in more than five subjects each. Since less than 25% of cases have been sequenced and subject choice was based on epidemiologic criteria and/or availability of samples, it is possible that single sequences may have a higher prevalence than indicated by their frequency within the INRB/UNMC cohort. Thus, they may be evaluating both the highest frequency sequences and a selection of GP variants represented only once in the cohort.

Due to recent attention given to sequences from a specific transmission chain in the Ituri Province, initial experiments focused on a sample of sequences from early, middle, and late in the Ituri outbreak as detailed below (Table 74).

Table 74. Virus GP Variants That Are Being Evaluated in Initial Experiments Presented in This Report

Item #	INRB/UNMC Seq. ID	Sample Date	GP Variations Relative to Ituri
1	Mayinga	1976	A3V/A310V/P368L/P377S/P422S/T429P/T432A/A435T/L443F/K458E/R478K/T544I
2	MAN046	8/15/2018	G557R
3	MAN4194	6/16/2019	V75A/E258K/T429A
4	MAN12309	12/3/2019	V75A/E258K/E280G/T429A

Source: Table 2, page 4, RIVV Study Report
Also noted are the date of isolation and the locations/residue differences in the GPs relative to the initial EBOV Ituri GP amino acid sequence.
Abbreviations: GP, glycoprotein; MAN, Mandima (Ituri province)

Compared with EBOV Mayinga, the initial EBOV Ituri consensus sequence exhibits 12 amino acid changes, with the majority of the changes found in the mucin-like domain (residues 368, 377, 422, 429, 432, 435, 443, 458) and additional changes located in the glycan cap (residue 310) and GP2 domain (residue 544) of GP. Over the course of the outbreak, additional changes were noted throughout all regions of GP1 and GP2. For MAN046, MAN4194, and MAN12309, the selected viruses have changes, relative to EBOV Ituri, in the GP1-core (residue 75), glycan cap (residues 258, 280), mucin-like domain (residue 429), and GP2 (residue 557). Of note, none of these substitutions occur near the ansuvimab-zykl epitope.

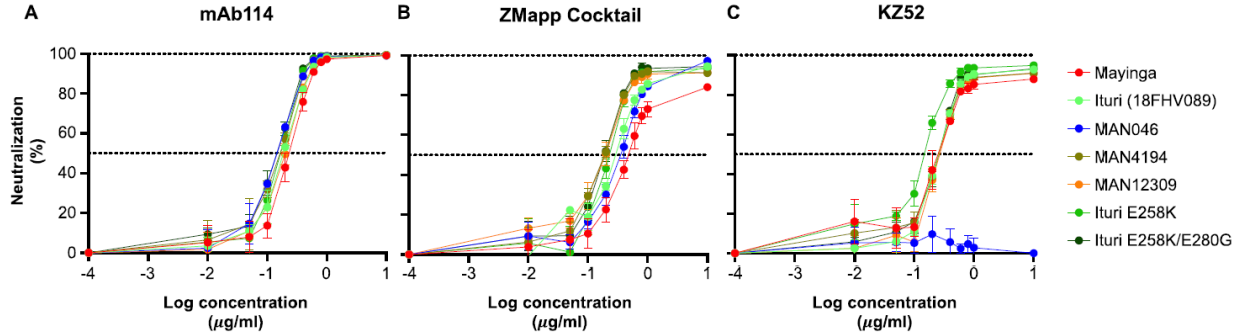
As a first test of GP-dependent entry, the Applicant determined the relative ability of each single-cycle lentivirus particle pseudotyped with the indicated EBOV variants to infect HEK293T cells. Viruses for each GP variant were titrated to infect the cells with comparable infectivity.

Single cycle virus entry into HEK293T was used to evaluate neutralizing activity of antibodies that target multiple antigenic surfaces in the RBD (ansuvimab-zykl), glycan cap (ZMapp cocktail), and GP1/GP2 base region (ZMapp cocktail and KZ52). To facilitate identification of both increases and decreases in the neutralization capacity across different viruses, a mAb concentration was chosen near the half maximal effective dose (0.1 μg/mL) using EBOV Mayinga as the reference.

The full dose-response confirmed that the antigenic surface of the RBD region remained intact in all virus variants, as the RBD targeting antibody, ansuvimab-zykl, showed no significant variations in their dose response curves (Figure 29). The glycan cap and antigenic surfaces in the base of the glycoprotein were evaluated using the ZMapp antibody cocktail and the monoclonal antibody, KZ52. For the Ituri virus variants, the ZMapp cocktail showed a similar increased potency of neutralization when compared to the reference Mayinga variant. This indicates that the antigenic surfaces targeted by ZMapp are not significantly altered by the variants. However, this conclusion may not account for an antigenic variation affecting one mAb in the cocktail that is offset by wildtype conformation at sites of the other two mAbs in the cocktail. Indeed, while the base binder KZ52 neutralization was generally not impacted by amino acid changes present within the Ituri variants, one variant (MAN046) was not neutralized by KZ52.

Since there is only one amino acid difference between MAN046 and Ituri (G577R), it suggests that the amino acid is impacting the antigenic surface in the base of the glycoprotein. Likely by the addition of a positively charged amino acid. These data are consistent with previous structural and functional data for KZ52, that show the antigenic surface near this position is critical to its binding to GP.

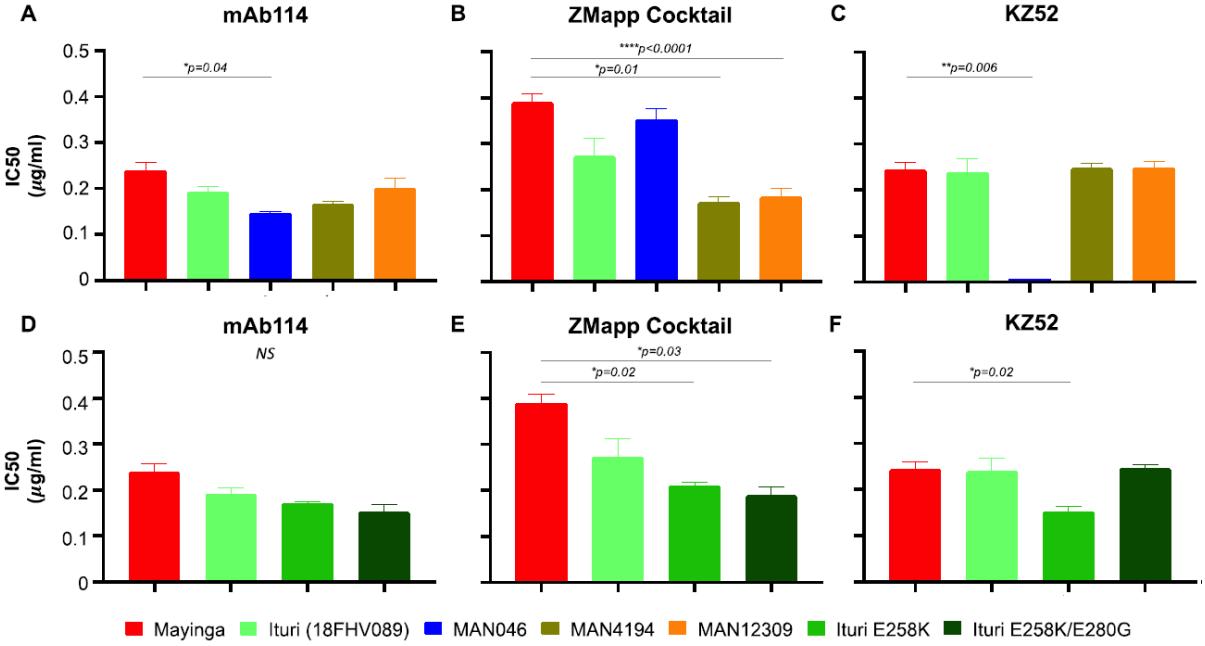
Figure 29. Monoclonal Antibody Neutralization Capacity Against the Different EBOV Variants



Source: Figure 8, page 10, RIVV Study Report
Neutralization was determined three days after infection by measuring relative luminescence units (RLU). The neutralization curve represents ten dilution points in series ranging from 10 µg/ml to 0.0001 µg/ml. Percent neutralization =100 - [(RLU with mAb)/(RLU with mAb at 0.0001 µg/ml)] x 100%, mean ± SD (n=3, representative experiment shown). Dotted lines represent respectively 50% and 100% neutralization.
Abbreviations: EBOV, *Zaire ebolavirus*

No statistical differences were observed between EBOV Mayinga and the initial EBOV Ituri sequences for all mAbs (Figure 30). Ansuvimab-zykl neutralized with similar activity for all EBOV variant viruses tested except for MAN046 with a higher potency (p=0.04). ZMapp neutralized with greater activity against EBOV variant viruses MAN4194, MAN12309, EBOV Ituri GP_E258K and EBOV Ituri GP_E258K/E280G compared to its EBOV Mayinga neutralization (p-values from 0.03 to <0.0001). KZ52 more efficiently neutralized EBOV Ituri GP_E258K (p=0.02) (Figure 30).

Figure 30. Half Maximal Effective Concentration (EC_{50}; Ordinate Labeled IC_{50}) Calculated for the Different mAbs Tested



Source: Figure 9, page 11, RIVV Study Report
(A and D) ansuvimab-zykl, (B and E) ZMapp cocktail, (C and F) KZ52 against the different Ebola variants, (A, B and C) Mayinga, Ituri (18FHV089), MAN046, MAN4194 and MAN12309, (D, E and F) Mayinga, Ituri (18FHV089), Ituri E258K and Ituri E258K/E280G. A four parameters logistic regression was used in order to obtain the EC_{50}. Statistical analyses were performed using repeated measures ANOVA on the mean ± SD (n=3, representative experiment shown). Only statistical differences observed between Mayinga and the other Ebola variants are depicted.
Abbreviations: NS, not statistically significant

Conclusion

EBOV variants from August 2018 (MAN046), June 2019 (MAN4194), and Dec 2019 (MAN12309) of the DRC 2018 EBOV outbreak were able to infect human cells to a similar degree as the initial EBOV Ituri (18FHV089) and EBOV Mayinga outbreak variants. Initial analysis of the antigenic surfaces via neutralization assays found that the antigenic surfaces bound by ansuvimab-zykl and ZMapp are mostly unchanged, as indicated by similar or improved neutralization activity against EBOV Mayinga, EBOV Ituri (18FHV089), MAN046, MAN4194, and MAN12309. However, KZ52 neutralization was similar in each of the variants except MAN046, likely reflecting a change to the antigenic surface bound by KZ52 in the base region of GP2.

Postmarketing Consideration

Resistance PMR #2

Conduct a study to identify all amino acid substitutions in the ansuvimab-zykl epitope (GP positions 111-119) and amino acids within 5 Angstroms from currently available EBOV GP sequences in public databases and perform phenotypic assessments to determine the impact that each of the substitutions have on ansuvimab-zykl neutralization using lentivirus-based particles pseudotyped with EBOV GP containing each of the substitutions. Please include EBOV GP substitutions L111I and L111F in your phenotypic analyses.

19. Other Drug Development Considerations: Additional Information and Assessment

Not applicable.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

Table 75. Clinical Inspection Summary

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

I. Overall Assessment Of Findings And Recommendations

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

II. Background

BLA 761172 was submitted in support of the use of ansuvimab-zykl (mAb114) for the treatment of *Zaire ebolavirus*. The key study supporting the applications was the following:

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

This was a multicenter, multi-outbreak, randomized, open-label, controlled clinical study, sponsored by NIAID, evaluating four 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, ansuvimab-zykl, and REGN- EB3) compared to the control arm, ZMapp.

Independent 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 December 12, 2018. On August 9, 2019, the DSMB recommended that patients be assigned only to the ansuvimab-zykl 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 ETUs in the Democratic Republic of the Congo
- *Study Initiation and Completion Dates:* November 20, 2018 to October 11, 2019
- *Database soft lock* occurred on November 5, 2019; *database hard lock* occurred on January 17, 2020

Eligible patients were stratified (by RT-PCR cycle threshold of≤22 versus >22), Ebola treatment unit, and outbreak) and randomized (in a 1:1:1:1 ratio) to one of the following four 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-zykl)
- 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 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 documents for the study were paper case report forms (CRFs), informed consent documents, and laboratory reports for safety labs and Ebola PCR results. Data were collected at the ETUs and transcribed onto paper 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 nine clinical investigators who rotated through, staffed, and supervised the conduct of the study for the four ETUs. Although only four of the nine clinical investigators, Drs. Jean-Luc Biampata, Ali Dilu, Isekusu Mpinda Fiston, and Vicky Malengera, were selected to represent the four ETUs during the inspections to answer questions, all nine 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 DRC, Drs. Biampata, Dilu, Fiston, and Malengera authorized inspections of the four ETUs (i.e., Beni, Katwa, Mangina, and Butembo) to be conducted at the NIAID in Bethesda, MD. NIAID provided inspectors access to the PALM Trial website (that contained scanned copies of the paper case report forms), the Huddle Database (that contained scanned copies of the informed consent documents and GeneXpert source records), and the REDCap electronic data capture (EDC) system used during the conduct of the trial (that contained the case report form data).

Because the Applicant 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 Trial 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: August 10-14, 2020

At this site for Protocol 19-I-0003, 337 subjects were screened, 335 were randomized (REGN-EB3, n=72; ZMapp, n=84; ansuvimab-zykl, 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), AE 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 AEs. 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 Applicant for the 173 subjects who were randomized to ZMapp (n=84) and ansuvimab-zykl (n=89). Survival status for the 90 subjects randomized to remdesivir was not reviewed. No discrepancies were noted.

Issues related to poor documentation were noted during inspection.

- 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.*

- 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 Applicant during the inspection. The Applicant stated that the missing source records were attributed to incomplete file upload to the HUDDLE database due to internet or to computers in the DRC that had malfunctioned or had been returned to donors. There was no documentation available regarding any corrective and preventative action (CAPA) that was taken.*

2. Ali Dilu, MD

Protocol 19-I-0003
Site Number: Katwa
Quartier Katwa, Commune Musosa
Katwa, Nord Kivu, Congo
Inspection Dates: August 10-14, 2020

At this site for Protocol 19-I-0003, 46 subjects were screened, 46 were randomized (REGN-EB3, n=10; ZMapp, n=12; ansuvimab-zykl, 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), AE 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 AEs. 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 Applicant for the 24 subjects who were randomized to ZMapp (n=12) and ansuvimab-zykl (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: August 10-14, 2020

At this site for Protocol 19-I-0003, 57 subjects were screened, 57 were randomized (REGN-EB3, n=14; ZMapp, n=13; ansuvimab-zykl, 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), AE 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 AEs. 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 Applicant for 28 subjects who were randomized to ZMapp (n=13) and ansuvimab-zykl (n=15). Survival status for the 15 subjects randomized to remdesivir was not reviewed. No discrepancies were noted.

4. Vicky Malengera, MD

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

At this site for Protocol 19-I-0003, 244 subjects were screened, 243 were randomized (REGN-EB3, n=63; ZMapp, n=60; ansuvimab-zykl, 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), AE 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 AEs. 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 Applicant for 120 subjects who were randomized to ZMapp (n=60) and ansuvimab-zykl (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

Office of Clinical Research Policy and Regulatory Operations (OCRPRO)
5601 Fishers Lane
Bethesda, MD 20892
Inspection Dates: August 10-14, 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, AE 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 Trial website, and the Huddle repository), AE 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 Trial 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 Trial 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 Trial 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 Trial 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 Applicant noted during the inspection that the SAE was expected as the Investigator's Brochure, Version 8.0, dated November 6, 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.*

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21. Labeling Summary of Considerations and Key Additional Information

Overview of Major Labeling Changes

- Information highlighted below are significant changes made to the prescribing information from the Applicant's proposed labeling submitted on June 9, 2019 for EBANGA (ansuvimab-zykl) with the to-be-approved USPI.
- HIGHLIGHTS and TABLE OF CONTENTS were revised for consistency with the full Prescribing Information.

Full Prescribing Information

1 INDICATIONS AND USAGE

- The indications statement was modified to add "the treatment of infection caused by *Zaire ebolavirus* including neonates born to a mother who is RT-PCR positive for *Zaire*

ebolavirus infection" because the proposed indication in adults and pediatric patients was non-specific for pediatric age group. Refer to Sections II.6.3.3 and II.6.3.4 for additional details.

- Limitations of Use (LOU) was added following precedent with influenza labeling which has similar LOU for viral infection that can change over time. Refer to Section II.6.3.4 for additional details. The following two LOUs were added:
  - The efficacy of EBANGA has not been established for other species of the *Ebolavirus* and *Marburgvirus* genera.
  - *Zaire ebolavirus* can change over time, and factors such as emergence of resistance, or changes in viral virulence could diminish the clinical benefit of antiviral drugs. Consider available information on drug susceptibility patterns for circulating *Zaire ebolavirus* strains when deciding whether to use EBANGA.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Adult and Pediatric Patients

The following additional detail on reconstitution was added: "EBANGA must be reconstituted with Sterile Water for Injection, USP then further diluted in 0.9% Sodium Chloride Injection, USP or Lactated Ringer's Injection, USP prior to IV infusion *[see Dosage and Administration (2.2)]*."

2.2 Preparation, Administration, and Storage Instructions

- Additional details were added to preparation, administration, and store instructions to mitigate potential medication errors. Applicant (b) (4) did not incorporate detailed information regarding preparation and administration in the USPI. Refer to Section II.7.1.1 for additional detail.
- Under dilution instructions, specific dilution instructions were provided for pediatric patients based on patient's weight, 0.5 to <2 kg and ≥2 kg, to mitigate potential medication error.
- Table 1: EBANGA Volume, Diluent Volume and Total Infusion Volume by Body Weight was added to provide clear instructions on how to dilute EBANGA solution based on patient's body weight, including the diluent volume, final infusion volume and infusion bag volume. (b) (4)
- Detailed administration instructions were added:
  - Prepare the IV infusion line with 1.2 micron in-line filter extension set.
  - Administer the IV infusion solution over approximately 60 minutes.
    - The diluted EBANGA IV solution can be infused via a central line or peripheral catheter.
      Do not administer EBANGA as an IV push or bolus.
    - Do not co-administer other drugs simultaneously through the same infusion line.
    - Infusions may be slowed or stopped if necessary, to alleviate any side effects.
- At the end of the infusion, if a syringe pump was used, then remove the syringe and flush the line with 2 to 5 ml of diluent, however, the flush volume should not exceed the total

infusion volume. If an infusion bag was used, replace the empty bag and flush the line by infusing at least 25 mL of the diluent, to ensure complete product administration.

- The Sponsor agreed to a PMC to conduct comprehensive compatibility and in-use stability studies to support administration conditions and materials described in the ansuvimab labeling and use of 5% dextrose as a diluent for neonates.

4 CONTRAINDICATIONS

- Applicant's proposed contraindication [redacted] (b) (4)

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Including Infusion-Associated Events

This warning was revised to add infusion-associated events during and post-infusion with EBANGA and recommendation to slow or interrupt infusion of EBANGA if the patient develops any signs of infusion-associated events or other adverse events. Refer to Section I.1 and Section II.7.6.3 for additional details.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

- Adverse reaction data was streamlined to show Table 2: Adverse Events That Occurred During Infusion in >10% of Adult and Pediatric Subjects in the PALM Trial comparing EBANGA (N=173) to control (N=168). The following statement, "The evaluation of adverse events in subjects who received EBANGA may have been confounded by the signs and symptoms of the underlying *Zaire ebolavirus* infection" was added. The adverse event profile in adult and pediatric subjects treated with EBANGA was similar. Refer to Section II.7.6.5 for additional details.
- The following pre-specified symptoms, which were assessed on a daily basis during admission while admitted to the treatment unit, were reported in ≥40% of subjects who received EBANGA: diarrhea, pyrexia, abdominal pain, and vomiting. Evaluation of these symptoms may have been confounded by the underlying Zaire ebolavirus infection. Refer to Section II.7.6.5 for additional details.
- Discontinuation and infusion rate adjustment: The following statement was added, "Two subjects who received EBANGA (1%) did not receive their complete infusion. In eight subjects (5%) the EBANGA infusion rate was decreased due to an AE *[see Warnings and Precautions (5.1)]*." Refer to Section II.7.6.1 for additional details.
- Selected laboratory abnormalities in the PALM trial: Table 3: Selected Grade 3 and 4 Laboratory Abnormalities, Worsened Grade from Baseline in the PALM Trial was added comparing EBANGA (N=173) with control (N=168). Refer to Section II.7.6.6 for additional details.

6.2 Immunogenicity

- Edits were made to this section to state that there are no data to assess the effects of potential immunogenicity on efficacy and safety in subjects with *Zaire ebolavirus* infection. Refer to Section II.7.7.3 for additional details.
- Due to suboptimal validation of the anti-drug antibody assay, immunogenicity data from the Phase I clinical study with healthy volunteers were not reported in the labeling. Refer to the immunogenicity assay review.

7 DRUG INTERACTIONS

7.1 Vaccine Interactions

The following language recommending avoiding concurrent administration of live vaccine during treatment with EBANGA was removed from Warnings and Precautions and added here. Refer to Section II.8.2 for additional details.

> **"**No vaccine-therapeutic interaction studies have been performed in human subjects using EBANGA. However, because of the potential for EBANGA to inhibit replication of a live vaccine virus indicated for prevention of *Zaire ebolavirus* infection and possibly reduce the efficacy of the vaccine, avoid the concurrent administration of a live vaccine during treatment with EBANGA. The interval between administration of EBANGA therapy and live vaccination should be in accordance with current vaccination guidelines. The efficacy of EBANGA among subjects who reported receipt of a recombinant live vaccine prior to their enrollment in the PALM trial was similar to subjects who did not report receiving a vaccine prior to enrollment."

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Summary of high rate of maternal and fetal/neonatal morbidity associated with underlying maternal *Zaire ebolavirus* infection was added based on PALM Trial, expanded access program (EAP), and published literature. Refer to Section II.8.4 for additional details.

Clinical Considerations

The following statement, "Treatment should not be withheld due to pregnancy" was added. Refer to Section II.8.4 for additional details.

8.2 Lactation

The following statement, "The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to ansuvimab-zykl are unknown" was added. Refer to Section II.8.4 for additional details.

8.4 Pediatric Use

This subsection was revised to state the safety and effectiveness of EBANGA for the treatment of infection caused by *Zaire Ebolavirus* have been established in pediatric patients birth to less than 18 years of age based on data from 54 pediatric subjects, including neonates born to a

mother who is RT-PCR positive for *Zaire Ebolavirus* based on the PALM trial. The 28-day mortality and safety in adults and pediatric subjects were similar. Refer to Section II.6.3.3 for additional details.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mechanism of action was modified to "Ansuvimab-zykl is a recombinant human monoclonal antibody with antiviral activity against *Zaire ebolavirus [see Microbiology (12.4)*]."

12.2 Pharmacodynamics

The following statement was added based on unknown E-R relationship, "Ansuvimab-zykl exposure-response relationship and the time course of pharmacodynamic response is unknown." Refer to Section II.6.1 for additional details.

12.3 Pharmacokinetics

(b) (4)

removed and summary statement that "Limited data from 18 healthy subjects 22 to 56 years of age suggests that the pharmacokinetic profile of ansuvimab-zykl is consistent with the profile of other IgG1 monoclonal antibodies." Refer to Section II.6.3.5 for additional details.

12.4 Microbiology

(b) (4)

The following information was added to subsection 12.4.

Mechanism of Action

Additional information regarding specific binding of ansuvimab to its receptor was added. Refer to Section II.5.1 for additional details.

Antiviral Activity

This subsection was rewritten to describe nonclinical antiviral activity assessments provided in the Application, to include neutralization activity and Fc-mediated effector functions. Refer to Section II.5.1 for additional details.

Resistance

This subsection was modified to indicate that clinical and nonclinical resistance data have not been received for ansuvimab. Refer to Section II.7.7.2 for additional details.

Immune Response

The following statement was added, "Interaction studies with recombinant live EBOV vaccines and EBANGA have not been conducted."

13 NONCLINICAL TOXICOLOGY

(b) (4)

14 CLINICAL STUDIES

- Description of the PALM Trial was revised to add:
  - Subject demographics was revised to add "neonates born to a mother who had cleared *Zaire ebolavirus* following a course of her assigned investigational medication were also eligible to be enrolled at investigator discretion regarding the likelihood that the neonate was infected."
- Table 4: Demographics and Baseline Characteristics in PALM Trial was added for EBANGA and control arms including age, sex, RT-PCR ctNP cycle threshold ≤22, median creatinine/ALT/AST/days from onset of symptoms to randomization and reported vaccination with rVSV-ZEBOV vaccine.
- Efficacy results were revised to present 28-day morality according to the demographics of subjects from Table 4. The mortality rate in the PALM Trial table was revised to present efficacy results with pediatric age groups and sex. Refer to Section II.6.2.4 for additional details.
- Kaplan-Meier curve was revised to show overall mortality (b) (4). Refer to Section II.6.2.4.2 for additional details.
- (b) (4) was removed because this was not the basis of approval.
- (b) (4) was removed because this was not the basis of approval. Refer to Section II.7.4 for additional details.

22. Postmarketing Requirements and Commitments

Below are the agreed upon PMRs (Table 76) and PMCs (Table 77) for this application. The CMC PMCs are detailed in Table 37.

Table 76. Agreed Postmarketing Requirements (PMRs)

PMR	Milestones
1. Conduct a study to identify all amino acid polymorphisms in the ansuvimab epitope (GP positions 111-119) and amino acids within 5 Angstroms from currently available *Zaire ebolavirus* (EBOV) GP sequences in public databases and perform phenotypic assessments to determine the impact that each of the substitutions have on ansuvimab neutralization using lentivirus-based particles pseudotyped with EBOV GP containing each of the substitutions. Also include EBOV GP substitutions L111I and L111F in your phenotypic analyses.	Study Completion: 09/2022 Final Report Submission: 03/2023
2. Conduct a study to identify ansuvimab resistance pathways using a recombinant virus expressing *Zaire ebolavirus* (EBOV) glycoprotein (GP) to select and characterize several independent resistant isolates phenotypically and genotypically.	Study/Trial Completion: 09/2022 Final Report Submission: 03/2023

Table 77. Agreed Postmarketing Commitments (PMCs)

PMC	Milestones
3. Submit all sequencing data that become available for patients who were treated with ansuvimab (mAb114) in the PALM and MEURI trials. Perform resistance analyses of these sequences and provide a study report discussing the approaches used and the resistance results generated.	Final Report Submission: 03/2023
4. Collaborate with US public health agencies, other public health agencies and local health authorities, as appropriate to design and conduct a trial to evaluate the efficacy, safety and pharmacokinetics of a higher dose of Ebanga (ansuvimab-zykl) vs. Ebanga 50 mg/kg in *Zaire ebolavirus* infected adult and pediatric patients with cycle-threshold (CT) values for nucleoprotein gene targets of less than or equal to 22 to determine if a change in dosing regimen is needed in these patients.	Final Protocol Submission: 12/2022
5. Submit a final report with complete, unblinded safety data for all subjects who were enrolled after interim results of the initial phase of the PALM Trial and were treated with ansuvimab-zykl (Ebanga) for *Zaire ebolavirus* infection during the PALM Extension Phase.	Final Report Submission: 06/2022
6. Conduct a tissue cross-reactivity study in human fetal tissues	Proposed Final Protocol Submission: 06/2021 Proposed Study Completion: 09/2021 Final Report Submission: 11/2021

23. Financial Disclosure

Ridgeback Biotherapeutics certifies that no financial arrangements with an investigator have been made where study outcome could affect compensation; that no investigator has a proprietary interest in the tested product; that no investigator has a significant equity interest in the sponsor of the covered study; and that the investigator has not received significant payments of other sorts, in compliance with 21 CFR Parts 54, 312, 314 and 601 (Form 3454). As clinical trials were sponsored by the Federal Government; investigators are not allowed payments of any sorts related to the conduct of the study. Tables 78, 79 and 80 provide the financial disclosures for the three studies submitted by the Applicant and reviewed in this BLA.

Table 78. Covered Clinical Studies: Phase 1 (NIH-19-I-0069)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Table 79. Covered Clinical Studies: Phase 2/3 PALM Trial (NIH-19-I-0003)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 9		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Table 80. Covered Clinical Studies: MEURI Expanded Access Protocol

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

24. References

Carroll, MWand DA Matthewsand JA Hiscoxand MJ Elmoreand G Pollakisand A Rambautand R Hewsonand I García-Dorivaland JA Boreand R Koundounoand S Abdellatiand B Afroughand J Aiyepadaand P Akhilomenand D Asogunand B Atkinsonand M Baduscheand A Bahand S Bateand J Baumannand D Beckerand B Becker-Ziajaand A Bocquinand B Borremansand A Bosworthand JP Boettcherand A Cannasand F Carlettiand C Castillettiand S Clarkand F Colavitaand S Diederichand A Donatusand S Duraffourand D Ehichioyaand H Ellerbrokand MD Fernandez-Garciaand A Fizetand E Fleischmannand S Gryseelsand A Hermelinkand J Hinzmannand U Hopf-Guevaraand Y Ighodaloand L Jamesonand A Kelterbaumand Z Kisand S Klothand C Kohland M Korvaand A Krausand E Kuismaand A Kurthand B Liedigkand CH Logueand A Lüdtkeand P Maesand J McCowenand S Mélyand M Mertensand S Meschiand B Meyerand J Micheland P Molkenthinand C Muñoz-Fontelaand D Muthand EN Newmanand D Ngaboand L Oestereichand J Okosunand T Olokorand R Omiunuand E Omomohand E Pallaschand B Pályiand J Portmannand T Pottageand C Prattand S Priesnitzand S Quartuand J Rappeand J Repitsand M Richterand M Rudolfand A Sachseand KM Schmidtand G Schudtand T Streckerand R Thomand S Thomasand E Tobinand H Tolleyand J Trautnerand T Vermoesenand I Vitorianoand M Wagnerand S Wolffand C Yueand MR Capobianchiand B Kretschmerand Y Halland JG Kennyand NY Rickettand G Dudasand CE Coltartand R Kerberand D Steerand C Wrightand F Senyahand S Keitaand P Druryand B Dialloand H de Clerckand M Van Herpand A Sprecherand A Traoreand M Diakiteand MK Kondeand L Koivoguiand N Magassoubaand T Avšič-Župancand A Nitscheand M Strasserand G Ippolitoand S Beckerand K Stoeckerand M Gabrieland H Raouland A Di Caroand R Wölfeland P Formenty and S Günther, 2015, Temporal

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25. Review Team

Table 81. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Andrew Gentles, PharmD, BCPS AQ-ID
Chief Project Management Staff	Linda Akunne, MPH
Nonclinical Reviewer (DPT-ID)	David McMillan, PhD, DABT
Nonclinical Team Leader (DPT-ID)	Christopher Ellis, PhD
Clinical Virology Reviewer	Eric Donaldson, PhD
Clinical Virology Team Leader	Julian O'Rear, PhD
Office of Clinical Pharmacology Reviewer(s)	Henrietta Abodakpi, PharmD, PhD
Office of Clinical Pharmacology Team Leader(s)	Su-Young Choi, PharmD, PhD
Clinical Reviewer	Samer El-Kamary, MD, MPH
Clinical Team Leader	Wendy Carter, DO
Statistical Reviewer	Wen Zeng, PhD
Statistical Team Leader	Thamban Valappil, PhD
Associate Director of Labeling	Stacey Min, PharmD
Cross-Disciplinary Team Leader	Wendy Carter, DO
Division Director (DPT-ID)	Hanan Ghantous, PhD, DABT
Division Director (OCP)	Kellie Reynolds, PharmD
Division Director (OB)	Dionne Price, PhD
Deputy Director for Safety	Poonam Mishra, MD, MPH
Division Director (clinical)	Debra Birnkrant, MD
Deputy Director (clinical)	Jeff Murray, MD, MPH
Office Deputy Director (OID)	Adam Sherwat, MD

OCP = Office of Clinical Pharmacology
OB = Office of Biostatistics

Table 82. Additional Reviewers of Application

Office or Discipline	Name(s)
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OPQ/OBP/IO	Vicky Borders Hemphill, PharmD
OPQ/OPRO	Marquita Burnett, MPH
OPDP	Nima Ossareh, PharmD, RAC
OSI	Cheryl Grandinetti, PharmD Phillip Kronstein, MD)Team Lead) Kassa Ayalew, MD, MPH (Branch Chief)
OSE/DEPI	
OSE/DMEPA	Valerie Vaughan, PharmD Sevan Kolejian, PharmD, MBA, BCPPS (Team Lead)
OSE/DRISK	
DPMH	Kristie Baisden, DO, FACOG Tamara Johnson, MD, MS (Team Lead)
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Medical Writer	Erica Boehm, PhD Hyo Sook Song Katharine Bradley
Other	

OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management

Table 83. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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Clinical	Samer El-Kamary, MD	OID/DAV	☒ Authored 1, 2, 3, 4, 6, 7, 8, 10, 11, 15, 17, 19, 20, 22, 23 ☐ Approved
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Clinical	Wendy Carter, DO	OID/DAV	☒ Authored contributed to 1, 16,17 ☒ Approved 1, 2, 3, 4, 6, 7, 8, 10, 11, 15, 16, 17, 19, 22, 23
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Regulatory	Andrew Gentles, PharmD, BCPS AQ-ID	OID/DRO-ID	☒ Authored 12 ☐ Approved
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Regulatory	Linda Akunne, MPH	OID/DRO-ID	☐ Authored ☒ Approved 12
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Clinical Virology	Eric Donaldson, PhD	OID/DAV	☒ Authored: II.5.1, II.6.3.4, II.7.7.2, III.18 Contributed to II.6.3.2 and III.22 ☐ Approved
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Clinical Pharmacology	Kellie Reynolds, PharmD	OTS/OCP/DIDP	☐ Authored ☒ Approved 5, 6.3.5, 7.2, 7.7.3, 8.1, 8.2 and 14
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Biometrics	Thamban Valappil, PhD	OTS/OB/DBIV	☐ Authored ☒ Approved 6.2, 6.3.1, 6.3.2, and 16
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Cross-Disciplinary	Stacey Min, PharmD	OID/DAV	☒ Authored 21 ☐ Approved
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Product Quality	Maria Gutierrez Lugo, PhD	OPQ/OBP/DBRR III	☐ Authored ☒ Approved 9
Branch Chief	**Signature:** Maria Teresa Gutierrez Lugo -S Digitally signed by Maria Teresa Gutierrez Lugo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011818863, cn=Maria Teresa Gutierrez Lugo -S Date: 2020.12.18 10:05:09 -05'00'		
Clinical	Tamara Johnson, MD, MS	OND/DPMH	☐ Authored ☒ Approved 8.4
Team Leader	**Signature:** Tamara N. Johnson -S Digitally signed by Tamara N. Johnson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300394304, cn=Tamara N. Johnson -S Date: 2020.12.17 12:53:09 -05'00'		
Clinical	Kristie Baisden, DO	OND/DPMH	☒ Authored 8.4 ☐ Approved
Primary Reviewer	**Signature:** Kristie W. Baisden -S Digitally signed by Kristie W. Baisden -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002275699, cn=Kristie W. Baisden -S Date: 2020.12.17 12:35:54 -05'00'		
Clinical	Gerri R. Baer, MD	OC/OCPP/OPT	☒ Authored 6.3.3; 7.7.3 ☒ Approved
Consult	**Signature:** Gerri Baer -S Digitally signed by Gerri Baer -S Date: 2020.12.17 14:15:44 -05'00'		

Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

ANDREW A GENTLES
12/21/2020 09:47:32 AM

ADAM I SHERWAT
12/21/2020 10:51:33 AM