HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EBANGA™ safely and effectively. See full prescribing information for EBANGA.

EBANGA™ (ansuvimab-zykl) for injection, for intravenous use Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
EBANGA (ansuvimab-zykl) is an *Orthoebolavirus zairense* glycoprotein (EBOV GP)-directed human monoclonal antibody indicated for the treatment of infection caused by *Orthoebolavirus zairense* in adult and pediatric patients, including neonates born to a mother who is RT-PCR positive for *Orthoebolavirus zairense* infection. (1)
Limitation of Use
- The efficacy of EBANGA has not been established for other species of the *Orthoebolavirus* and *Orthomarburgvirus* genera.
- *Orthoebolavirus zairense* 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 *Orthoebolavirus zairense* strains when deciding whether to use EBANGA.

----------DOSAGE AND ADMINISTRATION----------
The recommended dose of EBANGA for adult and pediatric patients is 50 mg/kg reconstituted, further diluted, and administered as a single intravenous infusion over 60 minutes. (2.1, 2.2)
See Full Prescribing Information for instructions on preparation, dilution and administration of EBANGA injection. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
For injection: 400 mg lyophilized powder in a single-dose vial for reconstitution and further dilution. (3)

----------CONTRAINDICATIONS----------
None.

----------WARNINGS AND PRECAUTIONS----------
Hypersensitivity Reactions Including Infusion-Associated Events: Hypersensitivity reactions including infusion-associated events have been reported with EBANGA. These may include acute, life-threatening reactions during and after the infusion. Monitor patients and in the case of severe or life-threatening hypersensitivity reactions, discontinue the administration of EBANGA immediately and administer appropriate emergency care. (5.1)

----------ADVERSE REACTIONS----------
The most frequently reported adverse events (≥ 5%) after administration of EBANGA were pyrexia, tachycardia, diarrhea, vomiting, hypotension, tachypnea, and chills. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Emergent BioSolutions at 1-800-768-2304 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Interaction with live vaccine indicated for prevention of *Orthoebolavirus zairense* infection: No vaccine interaction studies have been performed. EBANGA may reduce the efficacy of the live vaccine. The interval between administration of EBANGA therapy and live vaccination should be in accordance with current vaccination guidelines. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Patients infected with *Orthoebolavirus zairense* should be instructed not to breastfeed due to the potential for *Orthoebolavirus zairense* transmission. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EBANGA is indicated for the treatment of infection caused by *Orthoebolavirus zairense (formerly Zaire ebolavirus)* in adult and pediatric patients, including neonates born to a mother who is RT-PCR positive for *Orthoebolavirus zairense* infection *[see Dosage and Administration (2.2) and Clinical Studies (14)]*.

Limitations of Use:

The efficacy of EBANGA has not been established for other species of the *Orthoebolavirus* and *Orthomarburgvirus* genera.

Orthoebolavirus zairense 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 *Orthoebolavirus zairense* strains when deciding whether to use EBANGA.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Adult and Pediatric Patients

The recommended dosage of EBANGA is 50 mg/kg administered as a single intravenous (IV) infusion over 60 minutes. EBANGA must be reconstituted with Sterile Water for Injection, USP then further diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP prior to IV infusion *[see Dosage and Administration (2.2)]*.

2.2. Preparation, Administration, and Storage Instructions

EBANGA must be prepared and administered under the supervision of a health care professional.

Reconstitution Instructions

- Aseptically reconstitute and further dilute EBANGA prior to IV infusion. Do not administer as an IV push or bolus.
- More than one vial may be needed for a full dose. Calculate the dose (mg) based on the patient's actual weight in kg and the number of EBANGA vials required *[see Dosage and Administration (2.1)]*.
- Prior to reconstitution, allow EBANGA vial(s) to reach ambient temperature (15°C to 27°C [59°F to 81°F]) for approximately 20 minutes. If for any reason reconstitution cannot proceed immediately upon reaching ambient temperature, vials that have NOT been reconstituted may be kept at ambient temperature, protected from light, for no more than 24 hours.
- Immediately upon reaching ambient temperature, use a sterile 10 mL syringe and an 18-gauge needle to withdraw 7.7 mL of Sterile Water for Injection, USP. Insert the needle tip into the EBANGA vial. Holding horizontally, angle the needle down at an approximate 45° angle, above the lyophilized powder, which has a cake-like appearance. Slowly inject the diluent along the wall of the vial and without any air to avoid foaming and bubbles.
- Gently swirl (do NOT shake) for approximately 10 seconds; then set the vial down to rest for at least 10 seconds. Repeat until the cake is dissolved. This may take up to 20 minutes.

- Upon reconstitution, one vial delivers 8 mL of solution that is clear to slightly opalescent and colorless to slightly yellow containing 50 mg/mL of ansuvimab-zykl. Do NOT administer and discard the vial if the reconstituted solution is discolored or contains visible particles.
- Dilute the EBANGA solution immediately upon reconstitution. If needed, the reconstituted solution may be stored refrigerated at 2°C to 8°C (36°F to 46°F), protected from light, for up to 4 hours. This 4-hour window includes time required for further dilution and EBANGA solution should be infused immediately upon further dilution.

Dilution Instructions

- Following reconstitution, EBANGA must be further diluted prior to IV infusion.
    - Use an 18-20 gauge, 1-1.5" needle with an appropriately sized syringe up to 60 mL to perform the dilution steps.
    - Prepare the EBANGA IV dosing solution using an appropriately sized syringe up to 60 mL.
- For patients weighing ≥ 2 kg, prepare the diluent using either a latex-free, di-ethylhexylphthalate (DEHP)-free 0.9% Sodium Chloride Injection USP infusion bag, or latex-free, DEHP-free 5% Dextrose Injection USP infusion bag. For patients weighing 0.5 to < 2 kg use a pump-compatible syringe (Table 1).
    - For adult and pediatric patients, either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP can be used as the diluent.
    - The total volume of the infusion solution to be administered is based on the patient's body weight and is specified in Table 1.

  For patients weighing 0.5 to < 2 kg:
    - Use a 10 mL syringe compatible with the IV infusion pump.
    - Fill the 10 mL syringe with the appropriate amount of diluent (Table 1).
    - Add the calculated volume of EBANGA to the 10 mL syringe (Table 1).
    - Mix the diluted solution by gentle inversion (3 to 5 times) until admixed. Do not shake.

  For patients weighing ≥ 2 kg:
    - Select a diluent solution infusion bag size of appropriate fill volume based on the patient's body weight (see Table 1).
    - Withdraw and discard from the bag a volume of diluent solution that will leave remaining in the bag the appropriate volume based on the patient's weight (see Table 1). Then add the calculated volume of EBANGA to the bag based on the patient's weight (see Table 1).

      For example, for a 55 kg patient, withdraw and discard 150 mL of diluent from a 250 mL infusion bag. Then add 55 mL of EBANGA to obtain a total infusion volume of 155 mL.
    - Gently invert the IV bag 5 to 10 times until the diluted solution is admixed. Do NOT shake.
- Infuse the EBANGA solution immediately upon dilution. If needed, the diluted infusion solution may be stored refrigerated at 2°C to 8°C (36°F to 46°F), for up to 4 hours. Do not freeze the diluted solution. If refrigerated, allow approximately 20 minutes for the diluted solution to come to ambient temperature prior to use. These time limits include reconstitution time.
  Prepare a medical label including patient weight in kg, date, and time of reconstitution.
- Discard vial(s) and all unused contents.

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

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

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

[b] For IV bag administration, the diluent volume column includes the volume of diluent needed to remain in the infusion bag.

Administration

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not administer if discolored or if the vial contains visible particles.
- Do not mix with or administer as an infusion with other medicinal products.
- Prepare the IV infusion line with 1.2 micron in-line filter extension set.
- Administer the IV infusion solution over 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, but not to 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.

3 DOSAGE FORMS AND STRENGTHS

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.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Including Infusion-Associated Events

Hypersensitivity reactions including infusion-associated events have been reported with EBANGA. These may include acute, life-threatening reactions during and after the infusion. Monitor all patients

for signs and symptoms including, but not limited to, hypotension, chills and elevation of fever, during and following EBANGA infusion. In the case of severe or life-threatening hypersensitivity reactions, discontinue the administration of EBANGA immediately and administer appropriate emergency care *[see Adverse Reactions (6.1)].*

Infusion could not be completed in 1% of participants who received EBANGA due to infusion-associated adverse events. The rate of infusion of EBANGA may be slowed or interrupted if the patient develops any signs of infusion-associated events or other adverse events *[see Adverse Reactions (6.1)].*

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions Including Infusion-Associated Events *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice.

Overall, 424 adult and pediatric participants with *Orthoebolavirus zairense* infection received EBANGA in one clinical trial and as part of an expanded access program during the 2018 *Orthoebolavirus zairense* outbreak in the Democratic Republic of Congo (DRC).

In the PALM trial, the safety of EBANGA was evaluated in a multi-center, open-label, randomized controlled trial, in which 173 participants (119 adults and 54 pediatric participants) with confirmed *Orthoebolavirus zairense* infection received EBANGA as a single 50 mg/kg IV infusion and 168 participants received an investigational control *[see Clinical Studies (14)]*. All participants received optimized standard of care treatment (oSOC). The median age of the study population that received EBANGA was 26 years (range: 1 day to 85 years) and 55% were female.

During the same outbreak, 251 participants (173 adults and 78 pediatric participants) with laboratory- confirmed *Orthoebolavirus zairense* infection received EBANGA under an expanded access program, 57% of whom were female. Ages ranged from 6 days to 80 years, with a median age of 25 years.

Common Adverse Events

Table 2 summarizes the adverse events that were reported in the PALM trial from a pre-defined list of signs and symptoms that occurred during EBANGA infusion. The evaluation of adverse events in participants who received EBANGA may have been confounded by the signs and symptoms of the underlying *Orthoebolavirus zairense* infection. Twenty nine percent (n=51) of participants who received EBANGA in the PALM Trial experienced a pre-specified infusion-related adverse event. The most common pre- specified infusion-related adverse event reported in at least 10% of participants who received EBANGA was fever (Table 2). The adverse event profile in adult and pediatric participants treated with EBANGA was similar.

Table 2: Adverse Events That Occurred During Infusion in >10% of Adult and Pediatric Participants in the PALM Trial

Adverse Event[a]	EBANGA (N=173) %	Control[b] (N=168) %
Pyrexia	17	58
Tachycardia	9	32
Diarrhea[c]	9	18
Vomiting[c]	8	23
Hypotension	8	31
Tachypnea	6	28
Chills[d]	5	33
Hypoxia[c,]	3	11

[a]Adverse events in this table were reported on the day of infusion, and included signs and symptoms that occurred during or immediately after infusion

[b]Investigational therapy administered as three separate infusions

[c]Adverse events that occurred during infusion but were not pre-specified.

[d]The term chills includes other similar adverse events including rigors and tremors

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 participants who received EBANGA: diarrhea, pyrexia, abdominal pain, and vomiting. Evaluation of these symptoms may have been confounded by the underlying *Orthoebolavirus zairense* infection.

Discontinuation and Infusion Rate Adjustments

Approximately 99% of participants who received EBANGA in the PALM trial were able to complete their dose within one hour. Two participants who received EBANGA (1%) did not receive their complete infusion. In eight participants (5%) the EBANGA infusion rate was decreased due to an AE *[see Warnings and Precautions (5.1)]*.

Selected Laboratory Abnormalities in the PALM Trial

Table 3 presents selected laboratory abnormalities (worsening to Grade 3 or 4 compared to baseline) in the PALM trial.

Table 3: Selected Grade 3 and 4 Laboratory Abnormalities[a], Worsened Grade from Baseline in the PALM Trial

Laboratory Test[a]	EBANGA N=173 %	Control N=168 %
Sodium, high ≥ 154 mmol/L	5	4
Sodium, low < 125 mmol/L	7	11
Potassium, high ≥ 6.5 mmol/L	15	12
Potassium, low < 2.5 mmol/L	6	8
Creatinine (mg/dL) > 1.8 x ULN or ≥ 1.5 x baseline [b]	27	23
Alanine aminotransferase (U/L) ≥ 5 x ULN[c]	12	14
Aspartate aminotransferase (U/L) ≥ 5 x ULN[d]	13	18

ULN= upper limit of normal
[a] Graded per Division of AIDS (DAIDS) v2.1
[b] Based on a ULN of 1.2 mg/dL.
[c] Based on a ULN of 47 U/L.
[d] Based on a ULN of 38 U/L.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity from using ansuvimab-zykl. There are no data to assess the effects of potential immunogenicity on efficacy and safety in participants with *Orthoebolavirus zairense* infection.

7 DRUG INTERACTIONS

7.1 Vaccine Interactions

No vaccine-therapeutic interaction studies have been performed in human participants using EBANGA. However, because of the potential for EBANGA to inhibit replication of a live vaccine virus indicated for prevention of *Orthoebolavirus zairense* 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 participants who reported receipt of a recombinant live vaccine prior to their enrollment in the PALM trial was similar to participants who did not report receiving a vaccine prior to enrollment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Orthoebolavirus zairense infection is life-threatening for both the mother and fetus and treatment should not be withheld due to pregnancy *(see Clinical Considerations)*. Available data from the PALM trial in which pregnant women with *Orthoebolavirus zairense* infection were treated with EBANGA demonstrate the high rate of maternal and fetal/neonatal morbidity consistent with published literature regarding the risk associated with underlying maternal *Orthoebolavirus zairense* infection. These data are insufficient to evaluate for a drug associated risk of major birth defects, miscarriage, or adverse

maternal/fetal outcome.

Animal reproduction studies with ansuvimab-zykl have not been conducted. Monoclonal antibodies, such as EBANGA, are transported across the placenta; therefore, EBANGA has the potential to be transferred from the mother to the developing fetus.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Maternal, fetal and neonatal outcomes are poor among pregnant women infected with *Orthoebolavirus zairense*. The majority of such pregnancies result in maternal death with miscarriage, stillbirth, or neonatal death. Treatment should not be withheld due to pregnancy.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that mothers with confirmed *Orthoebolavirus zairense* not breastfeed their infants to reduce the risk of postnatal transmission of *Orthoebolavirus zairense* infection.

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

8.4 Pediatric Use

The safety and effectiveness of EBANGA for the treatment of infection caused by *Orthoebolavirus zairense* have been established in pediatric patients from birth to less than 18 years of age. Use of EBANGA for this indication is supported by evidence from a multi-center, open label, randomized controlled trial of EBANGA in adults and pediatric participants that included 54 pediatric participants birth to less than 18 years of age, including neonates born to a mother who is RT-PCR positive for *Orthoebolavirus zairense* infection. Of the total number of participants administered EBANGA in the PALM trial, pediatric participants (1 day to 17 years) accounted for 31% (n=54) of the study population in the PALM trial. The 28-day mortality and safety in adult and pediatric participants treated with EBANGA were similar *[see Adverse Reactions (6.1), and Clinical Studies (14)].* An additional 78 (31%) pediatric participants from birth to less than 18 years of age received EBANGA in an expanded access program.

8.5 Geriatric Use

Clinical trials of EBANGA did not include sufficient numbers of participants aged 65 and over to determine whether the safety profile of EBANGA is different in this population compared to younger participants. Of the total number of participants administered EBANGA in the PALM trial, 6 participants (3%) were 65 years or older. The limited clinical experience has not identified differences in responses between the elderly and younger participants.

11 DESCRIPTION

Ansuvimab-zykl is an *Orthoebolavirus zairense* (EBOV) glycoprotein 1 (GP1)-directed recombinant, human IgG1 monoclonal antibody. Ansuvimab-zykl is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology and has an approximate molecular weight of 147 kDa.

EBANGA (ansuvimab-zykl) for injection is a sterile, preservative-free, off-white to white lyophilized powder in a single-dose vial for IV use after reconstitution and dilution. Each single-dose vial delivers 400 mg of ansuvimab-zykl, and L-histidine (12.4 mg), L-histidine HCl (16.8 mg), polysorbate 80 (1.6 mg), and sucrose (657 mg). After reconstitution with 7.7 mL of Sterile Water for Injection, USP, each vial delivers 8 mL of a clear and colorless to slightly yellow solution containing 50 mg/mL of ansuvimab-zykl, with an approximate pH of 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ansuvimab-zykl is a recombinant human monoclonal antibody with antiviral activity against *Orthoebolavirus zairense [see Microbiology (12.4)*].

12.2 Pharmacodynamics

Ansuvimab-zykl exposure-response relationship and the time course of pharmacodynamic response is unknown.

12.3 Pharmacokinetics

Limited data from 18 healthy participants 22 to 56 years of age suggests that the pharmacokinetic profile of ansuvimab-zykl is consistent with the profile of other IgG1 monoclonal antibodies.

Pharmacokinetic data are not available for *Orthoebolavirus zairense* infected patients.

Specific Populations
The effect of age, renal impairment or hepatic impairment on the pharmacokinetics of ansuvimab-zykl is unknown.

12.4 Microbiology

Mechanism of Action
EBANGA (ansuvimab-zykl) is a recombinant, human IgG1κ monoclonal antibody that binds to the glycan cap and inner chalice of the EBOV GP1 subunit. The epitope to which it binds is located within the receptor binding domain of EBOV consisting of amino acids LEIKKPDGS (GP residues 111–119).

Ansuvimab-zykl binds EBOV GP without the mucin-like domain with a K_D of 0.2 nM at pH 7.4 and 0.6 nM at pH 5.3 as measured by biolayer interferometry. Ansuvimab-zykl blocks binding of EBOV GP1 to the Neiman Pick cell receptor 1 in host cells (half-maximal effective concentration (EC_{50}) value of 0.09 µg/mL), inhibiting virus entry into the host cell. Ansuvimab-zykl exhibited Fc-mediated Antibody Dependent Cellular Cytotoxicity (ADCC) activity against cells expressing EBOV GP when effector cells were added.

Antiviral Activity

In a live virus plaque-reduction neutralization assay performed in Vero E6 cells, ansuvimab-zykl neutralized *Orthoebolavirus zairense* Mayinga with an EC_{50} value of 0.06 µg/mL. In a pseudotyped EBOV GP lentivirus infectivity assay using HEK293 cells, ansuvimab-zykl inhibited *Orthoebolavirus zairense* Mayinga with an EC_{50} value of 0.09 µg/mL and *Orthoebolavirus zairense* Makona with an EC_{50} value of 0.15 µg/mL. The ADCC activity of ansuvimab-zykl was assessed in EBOV GP-transduced and non-transduced HEK293T target cells in the presence of antibody with effector cells added at an effector-to-target cell ratio 1:50 and analyzed via flow cytometry. Ansuvimab-zykl mediated ADCC, with maximal activity observed at mAb concentration of 0.03 µg/mL. Treatment of *Orthoebolavirus zairense* infected rhesus macaques with a single IV dose of ansuvimab-zykl (50 mg per kg) generally protected infected animals from *Orthoebolavirus zairense* mediated death when drug was administered 5 days post-infection.

Antiviral Resistance

No *in-vivo* nonclinical or clinical studies specifically evaluating resistance to ansuvimab-zykl have been conducted. The possibility of resistance to ansuvimab-zykl should be considered in patients who either fail to respond to therapy or who develop relapse of disease after an initial period of responsiveness.

Cell Culture Resistance

Ansuvimab-zykl cell culture resistance studies have been performed using replication competent recombinant vesicular stomatitis virus expressing the EBOV surface glycoprotein (rVSV-EBOV GP). The rVSV-EBOV GP virus was sequentially sub-cultured in six experiments for up to 5 passages in the presence of a concentration range of ansuvimab-zykl (0.08 to 50 µg/mL) to determine if escape mutants developed via selective pressure. A total of seven different amino acid substitutions in the EBOV GP were found (Table 4). Three of the seven were detected at less than 1% sequence frequency and were not within the ansuvimab-zykl GP epitope or within 5Å of the epitope, and therefore were excluded from further analysis.

Table 4: Identification of Ebola GP Substitutions in Cell Culture Studies

GP Substitutions	%Frequency of Sequences with the Substitution[a]	Ansuvimab-zykl Amino Acid Substitutions Induced at 50 µg/mL
R29S	<1	Excluded
P116H	71–94	Resistant
T144M	71–100	Resistant
N228H	<1	Excluded
R299K	71	No Resistance - Equivalent ansuvimab-zykl neutralization to Kikwit reference GP sequence
N434K	73	No Resistance - Equivalent ansuvimab-zykl neutralization to Kikwit reference GP sequence
T634A	<1	Excluded

[a] Frequency range of the sequences in 6 replicate experiments identified at the highest ansuvimab-zykl concentration of 50 µg/mL

The four remaining GP amino acid substitutions (P116H, T144M, R299K and N434K) were further evaluated in a single-cycle neutralization assay using a replication-defective lentiviral vector not

expressing envelope pseudotyped with EBOV GP containing each of the substitutions. The P116H and T144M substitutions exhibited resistance to ansuvimab-zykl based on no neutralization detected at the highest concentrations assessed (10 µg/mL) resulting in a >56-fold reduction in susceptibility for each substitution compared to the wild type EBOV GP.

Two additional substitutions within the EBOV GP conserved region (G118E and G118R), which were not found in the studies described above, have been reported in the literature from similar cell culture resistance studies and these substitutions were able to confer >29- and >34-fold reductions in susceptibility to ansuvimab-zykl, respectively.[1]

Of the four resistant substitutions identified under selective pressure in cell culture (P116H, G118E, G118R, and T144M), none have been identified in naturally infected Ebola virus disease patients.

In Clinical Studies

A post-hoc detailed analysis of currently available EBOV GP sequences in the public database (as of November 2022) was performed to identify all amino acid polymorphisms in the ansuvimab-zykl epitope (GP positions 111-119) and amino acids within 5Å of the epitope. A total of nine sequences out of 3324 available EBOV genomes had amino acid changes, of which two were within the ansuvimab-zykl linear epitope (L111I and L111F) and two within 5Å of the epitope compared to the Kikwit variant (I170L and I170F). Of the nine EBOV GP sequences, six were at the same amino acid location with the same amino acid substitution (I170L), one was at the same location as the previous six, but with a different amino acid substitution (I170F). The remaining two were at the same location but with different amino acid substitutions (L111I and L111F). Overall, four of the nine EBOV GP sequences expressed distinct amino acid substitutions at only two different positions. Phenotypic assessments of these amino acid changes inside of, or within 5Å of the ansuvimab-zykl linear epitope (111-119) using a pseudovirus neutralization assay were performed. The EBOV-GP pseudotyped viruses with the I170F and I170L substitutions were found to be inactive and unable to infect target cells. EBOV-GP pseudotyped viruses with the L111I and L111F were fully neutralized by ansuvimab-zykl with a potency similar to the Ituri wild type variant and historic Mayinga variant EC_{50} values and therefore none of the four identified amino acid substitutions are expected to be resistant to ansuvimab-zykl.

PALM Clinical study and MEURI EAP

Samples from a total of 95 participants (79 participants enrolled in the PALM randomized controlled clinical study and 16 participants from the MEURI EAP) including samples from 40 deceased participants and from 36 surviving participants with paired samples taken at baseline and after treatment with ansuvimab-zykl where available for EBOV glycoprotein (GP) sequencing. A total of 147 EBOV (GP) genome sequences were produced and when compared to the Kikwit or the Ituri reference sequences, no amino acid changes were found in the ansuvimab-zykl epitope or within 5Å of the ansuvimab-zykl epitope of EBOV GP. This finding includes EBOV GP sequences from deceased participants and samples collected after treatment with ansuvimab-zykl. When compared to the Kikwit and the Ituri variants, 26 and 14 amino acid substitutions, respectively, were found outside of the region of the ansuvimab-zykl epitope in EBOV GP from PALM participants. These amino acid changes were located predominantly in the less conserved mucin-like domain of the EBOV GP. None of these amino acid changes were associated with mortality nor appeared to be driven by ansuvimab-zykl treatment.

The amino acid substitution G118R, which was selected for in cell culture, was detected at 9% to 13% frequency by Next Generation Sequencing (NGS) in 10 participant samples (9 of which were

survivors) collected prior to treatment with ansuvimab-zykl in the PALM and MEURI EAP; the clinical significance of this substitution is unknown.

Immune Response

Interaction studies with recombinant live EBOV vaccines and EBANGA have not been conducted *[see Drug Interactions (7.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genotoxicity and fertility studies have not been conducted with ansuvimab-zykl.

14 CLINICAL STUDIES

The efficacy of EBANGA has been evaluated in 174 participants with confirmed *Orthoebolavirus zairense* infection in the PALM trial, a multi-center, open-label, randomized, controlled trial (NCT03719586). The trial was conducted in the North Kivu and Ituri provinces in the Democratic Republic of Congo, where an outbreak began in August 2018, and enrolled 681 participants of all ages, including pregnant women, with documented *Orthoebolavirus zairense* infection and symptoms of any duration who were receiving oSOC. Eligible participants had a positive reverse transcriptase-polymerase chain reaction (RT-PCR) for the nucleoprotein (NP) gene of *Orthoebolavirus zairense* and had not received other investigational treatments (with the exception of experimental vaccines) within the previous 30 days. Neonates ≤7 days of age were eligible if the mother had documented infection. Neonates born to a mother who had cleared *Orthoebolavirus zairense* 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. Participants were randomized to receive EBANGA 50 mg/kg IV as a single infusion, an investigational control 50 mg/kg IV every third day, for a total of 3 doses, or other investigational drugs. Randomization was stratified by reverse transcription-PCR cycle threshold calculated using NP targets (CtNP ≤22.0 vs >22.0; corresponding to high and low viral load, respectively) and Ebola Treatment Unit (ETU) site. All participants received oSOC consisting, at a minimum, of IV fluids, daily clinical laboratory testing, correction of hypoglycemia and electrolyte imbalances, and broad-spectrum antibiotics and antimalarials, as indicated.

The primary efficacy endpoint was 28-day mortality. The primary analysis population includes all participants who were randomized and concurrently eligible to receive either EBANGA or the investigational control during the same time period of the trial.

The demographics and baseline characteristics are provided in Table 5 below.

Table 5: Demographics and Baseline Characteristics in PALM Trial

Parameter	EBANGA N=174 N (%)	Control N=168 N (%)
Mean age (years)	27.3	29.9
Age <1 month, n (%)	4 (2)	2 (1)
Age 1 month to <1 year, n (%)	7 (4)	5 (3)
Age 1 year to <6 years, n (%)	15 (9)	12 (7)
Age 6 years to <12 years, n (%)	13 (7)	5 (3)
Age 12 years to <18 years, n (%)	15 (9)	9 (5)
Age 18 years to <50 years, n (%)	93 (53)	114 (68)
Age 50 years to <65 years, n (%)	21 (12)	18 (11)
Age ≥65 years, n (%)	6 (3)	3 (2)
Female, n (%)	98 (56)	87 (52)
Positive result on pregnancy test[a], n (%)	5/98 (5)	4/87 (5)
RT-PCR CtNP cycle threshold ≤22, n (%)	73 (42)	70 (42)
Median RT-PCR CtNP (IQR)	23.3 (19.7, 28.5)	23.1 (19.0, 26.5)
Median creatinine (IQR)	0.9 (0.6, 2.4)	1.2 (0.8, 4.3)
Median AST (IQR)	234 (66, 978)	351 (112, 1404)
Median ALT (IQR)	168 (44, 551)	236 (48, 631)
Median days from onset of symptoms to randomization (IQR)	5 (3, 7)	5 (3, 7)
Reported Vaccination with rVSV-ZEBOV vaccine, n (%)	36 (21)	41 (24)
<10 days before ETU admission, n (%)	22/36 (61)	21/41 (51)
≥10 days before ETU admission, n (%)	12/36 (33)	18/41 (44)
Timing unknown, n (%)	2/36 (6)	2/41 (5)

[a] Pregnancy positive test was calculated based on participants who were pregnant. Denominator for percentages is the number of females in the treatment group.
CtNP = cycle threshold calculated using NP targets; IQR=interquartile range; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; ETU=Ebola treatment unit.

The PALM trial was stopped early on the basis of a pre-specified interim analysis showing a statistically significant reduction in mortality for EBANGA compared to control assessed at Day 28.

Mortality efficacy results are shown in Table 6 and Figure 1.

Table 6: Mortality Rates in PALM Trial

Efficacy Endpoints	EBANGA[a] N=174	Control[a] N=168
Overall		
28-day mortality, n (%)	61 (35%)	83 (49%)
Mortality rate difference relative to control (95% CI)[b]	-14.3 (-24.7, -3.7)	
p-Value[c]	0.008	
Baseline Viral Load		
High viral load (CtNP ≤ 22)[d]		
28-day mortality, n (%)	51/73 (70%)	60/70 (86%)
Mortality rate difference relative to control (95% CI)[b]	-15.9 (-31.6, 0.9)	
Low viral load (CtNP > 22)[d]		
28-day mortality, n (%)	10/101 (10%)	23/97 (24%)
Mortality rate difference relative to control (95% CI)[b]	-13.8 (-27.3, 0.3)	
Age group, 28-day mortality, n/N (%)		
Adults (age ≥18 years)	41/120 (34%)	68/135 (50%)
12 to < 18 years of age	5/15 (33%)	5/9 (56%)
6 to < 12 years of age	4/13 (31%)	2/5 (40%)
< 6 years of age	11/26 (42%)	8/19 (42%)
Sex, 28-day mortality, n/N (%)		
Male	30/76 (39%)	32/81 (40%)
Female	31/98 (32%)	51/87 (59%)

N=Number of participants in the Concurrent Intention-to-Treat population and treatment group; n=Number of participants with the 28-day outcome. Denominator for percentages is the total number of participants in the specific group.

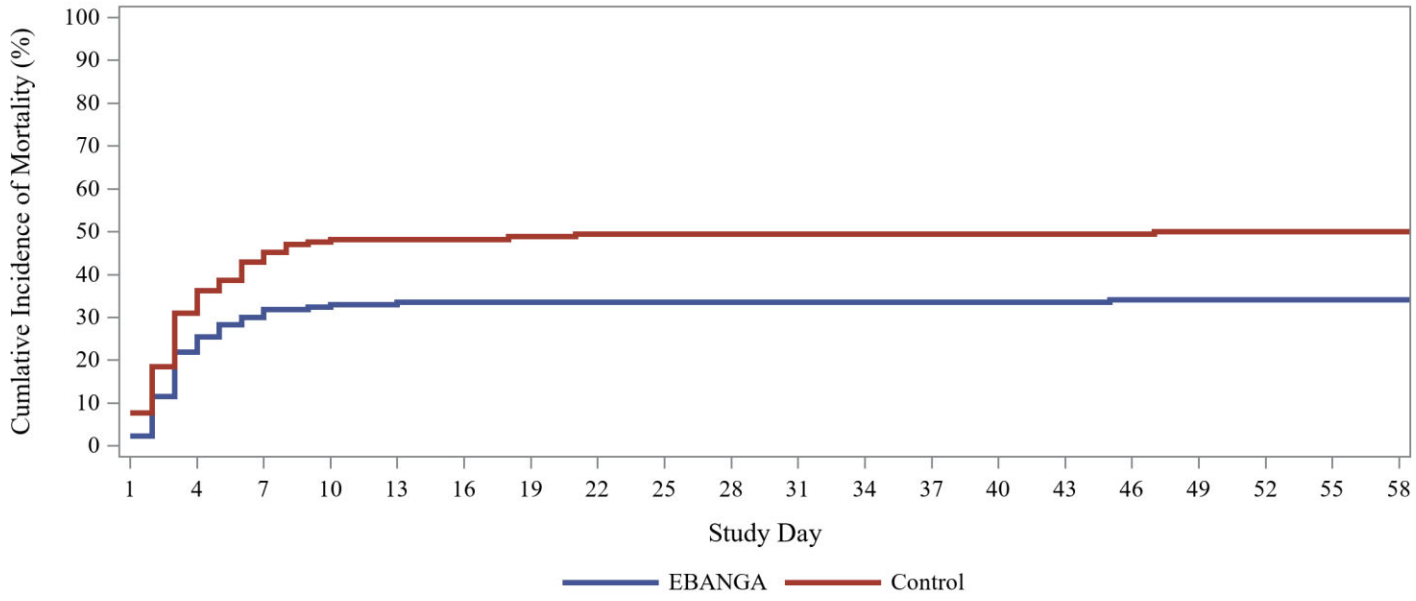
[a] Both EBANGA and Control were administered with optimized standard of care

[b] 95% CI for Difference = 95% confidence intervals were computed by inverting two one-sided exact tests.

[c] The result is significant according to the interim stopping boundary, p<0.028.

[d] Cepheid GeneXpert Ebola® Assay used for detection of *Orthoebolavirus zairense* RNA

Figure 1: Kaplan-Meier Curve for Overall Mortality in PALM Trial



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16 HOW SUPPLIED / STORAGE AND HANDLING

How Supplied

EBANGA (ansuvimab-zykl) for injection is supplied as a sterile, preservative-free, off-white to white lyophilized powder in a single-dose vial (NDC 71655-578-01) for reconstitution and further dilution.

One primary carton (NDC 71655-578-02) contains thirty-six 400 mg vials packaged in a box containing either one primary carton (NDC 71655-578-03), four primary cartons (NDC 71655-578-04), or eight primary cartons (NDC 71655-578-08).

Storage and Handling

Store refrigerated at 2ºC to 8ºC (36ºF to 46ºF) in the original carton to protect from light. Do not freeze. Do not shake.

Prior to reconstitution, allow EBANGA vial(s) to reach ambient temperature (15°C to 27°C [59°F to 81°F]) for approximately 20 minutes. If for any reason reconstitution cannot proceed immediately upon reaching ambient temperature, vials that have NOT been reconstituted may be kept at ambient temperature, protected from light, for no more than 24 hours.

After reconstitution, if storage is needed, the entire storage time for the reconstituted solution in the vial and the diluted solution in the IV bag should be protected from light and limited to 4 hours refrigerated at 2°C to 8°C (36°F to 46°F) *[see Dosage and Administration (2.2)]*.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions Including Infusion-Associated Events

Inform patients that hypersensitivity reactions including infusion-associated events have been reported during and post-infusion with EBANGA and to immediately report if they experience any symptoms of systemic hypersensitivity reactions *[see Warnings and Precautions (5.1)].*

Lactation

Instruct patients with *Orthoebolavirus zairense* not to breastfeed because of the risk of passing *Orthoebolavirus zairense* to the baby *[see Use in Specific Populations (8.2)].*

Manufactured by:

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