CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761172Orig1s000

PRODUCT QUALITY REVIEW(S)

Breakthrough/Priority Review
Recommendation: Approval

BLA Number: 761172
Review Number:1
Review Date: November 23, 2020

Drug Name/Dosage Form	EBANGA® [ansuvimab-zykl] for Injection
Strength/Potency	400 mg lyophilized powder in a single-dose vial
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	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
Applicant/Sponsor	Ridgeback Biotherapeutics, LP

Product Overview

Ebanga (ansuvimab-zykl, mAb114) is a recombinant human IgG1 monoclonal antibody targeting the Zaire ebolavirus (EBOV) surface glycoprotein (GP). Ebanga is produced in CHO cells from a clone derived from a memory B cell clone isolated from the blood of a 1995 Ebola Virus Disease outbreak survivor. Ebanga neutralizes EBOV infectivity by binding to the glycan cap and core domains of the EBOV GP, thereby preventing interaction of GP with the host Niemann-Pick C1 receptor, and subsequently inhibiting virus-host cell fusion and viral entry into the cell cytoplasm. Ebanga also exhibits antibody-dependent cell mediated cytotoxicity (ADCC) activity in vitro. Ebanga is indicated for the treatment of infection caused by Zaire ebolavirus in adult and pediatric patients, including neonates born to an infected mother. Ebanga drug product is supplied as a sterile preservative-free, off-white to white lyophilized powder in a 20 mL (b) (4) glass vial containing 400 mg of ansuvimab per vial.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Davinna Ligons/Frances Namuswe	DBRRIII/OBP
Drug Product	Davinna Ligons/Frances Namuswe	DBRRIII/OBP
Microbiology Drug Substance	Yun Wu/ Maria Candau-Chacon	DBM/OPMA
Microbiology Drug Product	Virginia Carroll/ Maria Candau-Chacon	DBM/OPMA
Facility	Yun Wu/Zhihao Peter Qiu	DBM/OPMA
Labeling	Vicky Borders-Hemphill	IO/OBP
Immunogenicity	Davinna Ligons/Frances Namuswe	DBRRIII/OBP
Application Team Lead	Frances Namuswe	DBRRIII/OBP
Application Tertiary reviewer	Maria Teresa Gutierrez-Lugo	DBRRIII/OBP
OPQ RBPM	Marquita Burnett	OPRO/DRBPMI/RBPMB

Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
OND RPM	Andrew Gentles	OND/ORO/DROID
Cross-disciplinary Team Lead	Wendy Carter	OND/OID/DAV
Medical Officer	Samer El-Kamary/ Wendy Carter	OND/OID/DAV
Pharm/Tox	David McMillan/Christopher Ellis	OND/OID/DPT-ID
Clinical Virology	Eric Donaldson/ Julian O'Rear	OND/OID/DAV
Clinical Pharmacology	Henrietta Abodakpi/Su-Young Choi	OTS/OCP/DIDP
Statistics	Wen Zeng/ Thamban Valappil	OTS /OB/DBIV
DMEPA	Valerie Vaughan/Sevan Kolejian	DMEPA/OSE

1. Names:
   - a. Proprietary Name: EBANGA
   - b. Trade Name: EBANGA
   - c. Non-Proprietary/USAN: ansuvimab-zykl
   - d. CAS name and number: 2375952-29-5
   - e. Common name:
   - f. INN Name: ansuvimab-zykl
   - h. OBP systematic name: MAB HUMAN (IGG1) ANTI P60171 (VSGP_EBOZ5) [ANSUVIMAB]
   - i. Other names: mAb114
     Immunoglobulin G1, anti-(Zaire ebolavirus glycoprotein glycan cap and GP1 domain) (human monoclonal mAb114 γ1-chain), disulfide with human monoclonal mAb114 K chain, dimer

2. Pharmacological class: Zaire ebolavirus glycoprotein (EBOV GP)-directed human monoclonal antibody

Submissions Reviewed

Submission #:	Date Received:	Submission Type
STN 761172/0002	March 10, 2020	Module 3 pre-submission "Wave 2"
STN 761172/0003	March 12, 2020	Module 3 pre-submission "Wave 2b"
STN 761172/0004	April 1, 2020	Module 3 pre-submission "Wave 3"
STN 761172/0005	April 15, 2020	Response to Product Quality IR
STN 761172/0006	April 20, 2020	Response to Product Quality IR
STN 761172/0007	April 30, 2020	Module 3 pre-submission "Wave 5"
STN 761172/0008	May 29, 2020	Original BLA Submission
STN 761172/0010	June 18, 2020	Response to Product Quality IR
STN 761172/0011	June 19, 2020	Response to Product Quality IR
STN 761172/0013	July 15, 2020	Response to Product Quality IR
STN 761172/0014	July 16, 2020	Response to Product Quality IR
STN 761172/0015	July 29, 2020	Product Quality Information Update
STN 761172/0018	August 28, 2020	Response to Product Quality IR
STN 761172/0019	September 01, 2020	Response to Product Quality IR
STN 761172/0020	September 02, 2020	Response to Product Quality IR
STN 761172/0021	September 03, 2020	Product Quality Update after PLI

STN 761172/0025	September 28, 2020	Response to Product Quality IR
STN 761172/0026	September 29, 2020	Response to Immunogenicity IR
STN 761172/0027	September 30, 2020	Response to Product Quality IR
STN 761172/0028	October 01, 2020	Labeling
STN 761172/0029	October 02, 2020	Product Quality Information
STN 761172/0030	October 05, 2020	Response to Product Quality IR
STN 761172/0031	October 07, 2020	Request for Exception from 21 CFR Labeling Requirements
STN 761172/0032	October 09, 2020	Response to Product Quality IR
STN 761172/0033	October 15, 2020	Response to Product Quality IR
STN 761172/0034	October 15, 2020	Response to Product Quality IR
STN 761172/0035	October 15, 2020	Labeling
STN 761172/0036	October 16, 2020	Response to Product quality IR
STN 761172/0037	October 16, 2020	Response to Product quality IR
STN 761172/0038	October 16, 2020	Response to Product Quality IR
STN 761172/0039	October 19, 2020	Response to Product Quality IR
STN 761172/0040	October 22, 2020	Response to Product Quality IR
STN 761172/0041	October 28, 2020	Response to Product Quality IR
STN 761172/0042	October 29, 2020	Response to Product Quality IR
STN 761172/0043	October 30, 2020	Response to Product Quality IR
STN 761172/0044	November 02, 2020	Labeling
STN 761172/0045	November 02, 2020	Request for Labeling Exception
STN 761172/0046	November 03, 2020	Response to Product Quality IR
STN 761172/0047	November 06, 2020	Response to Product Quality IR
STN 761172/0048	November 09, 2020	Response to Product Quality IR
STN 761172/0050	November 16, 2020	Response to Product Quality IR
STN 761172/0051	November 18, 2020	Response to Product Quality IR
STN 761172/0052	November 18, 2020	Response to Product Quality IR
STN 761172/0054	November 19, 2020	Response to Product Quality IR
STN 761172 /0055	November 23, 2020	Labeling
STN 761172 /0057	November 23, 2020	PMCs
STN 761172 /0058	November 24, 2019	Response to Product Quality IR
STN 761172 /0059	November 25, 2020	Response to Product Quality IR
STN 761172 /0060	November 25, 2020	Response to Product Quality IR
STN 761172 /0061	December 2, 2020	Response to Product Quality IR; Labeling
STN 761172 /0062	December 2, 2020	Response to Product Quality IR; Request for Exception from 21 CFR Labeling Requirements
STN 761172 /0063	December 7, 2020	Response to Product Quality IR
STN 761172 /0064	December 10, 2020	Labeling
STN 761172 /0065	December 10, 2020	Request for Exception from 21 CFR Labeling Requirements
STN 761172 /0067	December 14, 2020	Response to Product Quality IR
STN 761172 /0068	December 15, 2020	Request for Exception from 21 CFR Labeling Requirements
STN 761172 /0069	December 15, 2020	Response to Product Quality IR
STN 761172 /0070	December 15, 2020	Response to Product Quality IR
STN 761172 /0071	December 16, 2020	Response to Product Quality IR
STN 761172 /0072	December 16, 2020	Response to Product Quality IR

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents

A. DMFs

DMF#	DMF Type	DMF Holder	Item Referenced	Code[1]	Date Assessment completed	Comments (status)
(b) (4)	V	(b) (4)		3	N/A	Review not needed. Relevant information was submitted in the BLA.
	III			1 3	3/6/2020 and 10/7/2020	Reviewed and found adequate from a sterility assurance perspective Relevant information regarding compatibility with product was submitted in the BLA.
	III			3		Review not needed. Relevant information regarding compatibility with the product was submitted in the BLA.
	III			2	11/1/2019	Adequate
	V			2	4/25/2017 (b) (4))	Adequate
	V			2	3/5/2020 and 6/22/2020	Adequate

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows: 2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Application Number	Description
IND 138090	mAb114

3. Consults

None issued.

4. Environmental Assessment or Claim Of Categorical Exclusion

Ridgeback Biotherapeutics claims categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(b) because the estimated concentration of Ebanga at the point of entry into the aquatic environment is ≈ (b) (4) ppb, which is significantly lower than the 1 ppb threshold. Per 21 CFR 25.31(b) and 21 CFR 25.31(c), categorical exclusion can be granted for Ebanga. Therefore, the claim of categorical exemption for Ebanga is accepted.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality (OPQ), CDER recommends approval of BLA 761172 for Ebanga manufactured by (b) (4) 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.

B. Approval Action Letter Language

- Manufacturing location:
  - **Drug Substance and Drug Product manufacture**: (b) (4)

    DP labeling and Secondary packaging: (b) (4)
- Fill size and dosage form: 400 mg lyophilized powder in a single-dose vial for injection
- Dating period:
  - Drug Product: 12 months at 2-8°C
  - Drug Substance: (b) (4) months a (b) (4) C
  - For packaged Products: Not Packaged
  - Stability option:
    - Limited stability data
      - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
    - Stability protocols
      - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

- Exempt from lot release
  - Yes. Ebanga is exempted from lot release per Docket No 95-29960 because it is a well characterized recombinant monoclonal antibody.

C. Benefit/Risk Considerations

Ebanga received orphan drug designation, breakthrough designation, and priority review status for the treatment of infection caused by Zaire ebolavirus in adult and pediatric patients, including neonates born to infected mothers. Zaire ebolavirus is highly infectious and leads to rapidly progressive and often fatal disease. The spread of the 2014 to 2016 West Africa outbreak internationally, including 11 reported cases in the US, caused considerable international concern and the disease remains a global threat to public health. Inmazeb, a mixture of three monoclonal antibodies, atoltivimab, maftivimab, and odesivimab-ebgn, recently (October 14, 2020) became the first FDA-approved treatment for Zaire ebolavirus infection in adult and pediatric patients, and is the only FDA approved therapy currently available. In addition, there is one recent FDA-approved vaccine (December 19, 2019) for the prevention of Zaire ebolavirus infection. However, the vaccine cannot treat existing infections. Therefore, availability of another effective, well-tolerated therapy that can be used for patients of any age is highly desirable.

Ebanga was assessed as one of four investigational therapies in the PAmoja TuLinde Maisha (PALM) multi-center, randomized controlled study (the same trial used to support approval of Inmazeb). Data from the PALM study show that treatment of Zaire ebolavirus infection with a 50 mg/kg single dose of Ebanga resulted in clinically meaningful and statistically significant lower mortality (35.1%) compared to the active comparator, ZMapp at Day 28 (49.4%, p=0.008). Additional supportive data from a non-controlled study, the MEURI Expanded Access Program, demonstrated similar efficacy as the PALM study, showing that treatment with Ebanga led to a mortality rate of 32.3% at 21 days compared to the mortality rate of 66% in untreated patients.

The data submitted in this application are sufficient to demonstrate that the manufacture of Ebanga is well-controlled and leads to a product that is safe, pure and potent. Therefore, from a product quality perspective, this product is approvable for human use as described in the product labeling. Of note, product development of Ebanga was abbreviated due to positive interim analysis results from the PALM study and the urgent need for effective treatments for Ebola virus infections. Therefore, agreements were made to complete several product and process characterization studies post-approval. The Applicant agreed to several post-marketing commitments (PMCs) to improve the robustness of the drug substance (DS) and drug product (DP) manufacturing processes and overall product control strategy as outline in Section D below. In addition, several protocols for post-approval studies are approved with the BLA.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

The following post marketing commitments have been proposed and accepted by the Applicant:

Microbiology

3965-7: Qualify the bioburden test method for the (b) (4) with 3 batches of product using 10 mL samples

Final Report Submission: 12/2022.

3965-8: 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.

3965-9: 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.

3965-10: 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.

Product Quality

3965-11: 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 date: 03/2022

3965-12: 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 date: 03/2021

3965-13: 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 date: 03/2022

3965-14: 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 date: 03/2022

3965-15: 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 date: 03/2022

3965-16: 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 date: 03/2022

3965-17: To 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 demonstrate that ADCC activity contributes to the mechanism of action, update the control strategy to ensure that ADCC activity is sufficiently 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 date: 03/2022

3965-18: 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 date: 03/2022

3965-19: 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 date: 03/2022

II. Summary of Quality Assessments

Because product development of ansuvimab was abbreviated, the identification of critical quality attributes (CQAs), risk assessments, and lifecycle knowledge management are based on limited product and process knowledge. The Applicant was advised to conduct more comprehensive product characterization studies post-approval to update the control strategy and to support future comparability assessments. The additional product and process characterization studies will further improve these assessments.

Table 1 and Table 2 summarize the CQAs intrinsic to ansuvimab API and the drug substance manufacturing process, respectively. These CQAs are based on both the Applicant determined presumptive CQAs and quality attributes generally considered CQAs for this class of products, regardless of how they were classified by the Applicant.

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy (additional comments)
Identity (General)	Safety and Efficacy	Intrinsic to the molecule	(b) (4)
Primary Structure	Efficacy and Immunogenicity	- Intrinsic to the molecule - Expression construct and cell line	

Higher Order Structure	Efficacy and Immunogenicity	- Intrinsic to the molecule	(b) (4)
EBOV Neutralization (Potency)	Efficacy	- Intrinsic to the molecule - May be impacted by the DS manufacturing process and product related impurities	PMC to develop a viral neutralization potency assay
ADCC Activity (potency)	Potential impact on Efficacy (undetermined contribution to MOA)	- Intrinsic to the molecule - Impacted by afucosylated glycans and DS manufacturing process	(b) (4) PMC to further characterize the potential contribution of ADCC activity to MOA, assess all clinical and PPQ lots for ADCC activity, and update the control strategy as needed.
Glycosylation	Potential impact on Efficacy through ADCC activity and/or PK	- Intrinsic to the molecule - Affected by the DS manufacturing process	(b) (4)
Heavy and Light Chain (Purity)	Efficacy and Safety	- DS manufacturing process	
Aggregates (product impurities)	Efficacy and Safety	- Manufacturing process - May increase on storage	
Fragments (product impurities)	Efficacy and Safety	- Manufacturing process - May increase on storage	
Acidic and basic variants (product variants)	Potential impact on Efficacy and Safety	- Intrinsic to the molecule - DS and DP manufacture - May increase on storage	

B. Ebanga [ansuvimab-zykl] Drug Substance Quality Summary

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy (additional comments)
Appearance (general)	Safety	- DS Manufacturing process	(b) (4)
Identity (general)	Efficacy and Safety	-Intrinsic to the molecule	
pH (general)	Safety and DS stability	- DS manufacturing	

Protein Content (general)	Efficacy	- DS manufacturing	(b) (4)
Osmolality (general)	Patient Discomfort (since no DS dilution to generate DP)	- DS manufacturing	
(b) (4)	Product Stability	- DS manufacturing	PMC to develop and implement a more robust control strategy fo (b) (4) in DS and DP
Host Cell Proteins (process impurity)	Safety and immunogenicity	(b) (4)	(b) (4) PMC to assess coverage of the HCP assay to confirm sensitivity
Host Cell DNA (Process impurity)	Safety		(b) (4)
(b) (4) (Process Impurity)	Safety and immunogenicity		
Adventitious virus (Contaminant)	Safety	Raw materials and contamination during manufacturing	PMC to conduct additional viral clearance studies using four relevant model viruses
Mycoplasma (Contaminant)	Safety	Raw materials and contamination during manufacturing	(b) (4)
Bioburden (Contaminant)	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process	
Endotoxin (Contaminant)	Safety and purity	Endotoxin can be introduced by raw materials and throughout the manufacturing	
(b) (4)	Safety	DS manufacture	

(b) (4) (Process impurities)			PMC to conduct studies to confirm clearance of process related impurities by DS manufacturing process
Leachables (Impurities)	Safety and product stability	Manufacturing equipment and container closure	(b) (4) PMC to perform extractables/leachables studies and risk assessments

a. Description

Ebanga (ansuvimab-zykl) is an anti-EBOV GP human IgG1 monoclonal antibody produced in CHO cells. It contains a typical IgG monoclonal antibody structure with 449 amino acids in the heavy chain, 214 in the light chain, a total of 8 intra- and inter-chain disulfide bonds, an N-linked glycosylation site at N299, and a molecular weight of 147 kDa.

b. Mechanism of Action (MoA)

Ebanga is indicated for the treatment of infection caused by Zaire ebolavirus in adult and pediatric patients, including neonates born to an infected mother. Entry of EBOV into host cells is facilitated by its surface glycoprotein (GP), which consists of two subunits, GP1 and GP2. Once internalized into host cells, EBOV GP is cleaved in the endosome to remove the mucin and glycan cap of GP1 thus exposing the receptor binding site on GP1. The exposed binding site interacts with host Niemann-Pick C1 (NPC1) protein to form a complex that facilitates fusion of the viral and host-cell membranes allowing viral entry into the cell cytoplasm.

According to the Applicant and published literature, Ebanga binds to an epitope spanning the glycan cap and core domains of EBOV GP1. It binds with high affinity to both the intact GP and the endosomal cleaved form of GP (GPCL) at neutral and acidic pH conditions, and it remains bound to the core domain after removal of the glycan cap. The high affinity binding to GPCL at low pH allows Ebanga to stay bound to the virus in the acidic endosome, thereby blocking the GPCL-NPC1 interaction and inhibiting virus-host cell fusion.

Ansuvimab also exhibits ADCC activity in vitro; however, its role in the mechanism of action has not been fully determined. The Applicant agreed to a PMC to further characterize the role of ADCC activity in Ebanga's mechanism of action.

c. Potency Assay

The current potency assay measures binding of Ebanga to the GP protein by ELISA. GP coated plates are incubated with serially diluted DS or DP samples, assay control, and standard. Bound Ebanga is detected and quantified using a horse radish peroxidase conjugated secondary antibody followed by incubation with TMB substrate. The observed OD is plotted against nominal concentration and fit using a 4-PL fit. Binding activity of the sample is determined relative to that of a reference standard as the ratio of their EC_{50} values. Percent potency is reported relative to the reference standard. The Applicant established an adequate link between the potency assay proposed for commercial use and other potency assays used to release clinical material. The

Applicant also agreed to a PMC to develop and implement a validated cell-based viral neutralization potency assay that better reflects Ebanga's mechanism of action.

(b) (4) The Sponsor agreed to a PMC to update the control strategy for ADCC activity as needed.

d. Reference Materials

(b) (4)

(b) (4) Protocols for qualification of future primary and working reference standards and requalification of all reference standards are approved as part of this BLA.

e. Critical starting materials or intermediates

(b) (4)

f. Manufacturing process summary

(b) (4)

(b) (4)

The manufacturing process is validated and controlled through defined operating and performance parameters supported by the process performance studies for two PPQ lots, and supporting data for one GMP lot manufactured with the same process. To further confirm consistency of the DS manufacturing process, per pre-BLA agreements, a complete final report that includes at least one additional PPQ DS lot manufactured according to an Agency approved prospective process validation protocol will be submitted post approval.

g. Container closure

DS is stored in (b) (4)

h. Dating period and storage conditions

Ebanga DS is stored at (b) (4) C. The data support a shelf life of (b) (4) months under these storage conditions. A protocol to extend the shelf life is approved with the BLA.

C. Drug Product Ebanga [ansuvimab-zykl] Quality Summary:

Table 3 provides a summary of the CQAs that derive from the drug product manufacturing process and general drug product attributes, their origin and associated risk, and control strategy.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy (additional comments)
Appearance, before & after reconstitution (General)	Safety, Efficacy, product stability	Formulation, contamination, lyophilization, or degradation	(b) (4)
Identity	Safety and Efficacy	Intrinsic to the molecule	
Sterility (Contaminant)	Safety risk to patients (infection), efficacy (degradation or modification of the product by microorganisms or	Contamination could be introduced throughout the DP manufacturing process or through a container closure integrity failure	

	their byproducts)		(b) (4)
Endotoxin (Contaminant)	Safety, purity and immunogenicity	Contamination could be introduced throughout the DP manufacturing process or through a container closure integrity failure	PMC to develop an alternative endotoxin method to mitigate low endotoxin recovery (LER) and submit the LER study report
Container Closure Integrity (Sterility Assurance)	Safety (loss of sterility due to breaches in CCI)	Storage conditions	(b) (4) PMC to implement a validated container closure integrity test in lieu of the sterility test
Particulate Matter: Visible and Sub-Visible Particulates (General)	Safety and Immunogenicity	Particulates can be introduced by the manufacturing process, container closure system, or during reconstitution	(b) (4)
pH of reconstituted product) (General)	Stability	- DS manufacture since there is no additional formulation during DP manufacture	
Leachables (Impurities)	Safety and product stability	Manufacturing product contact equipment and container closure system	PMC to perform leachables & extractables studies to confirm the conclusions above
Extractable volume - after reconstitution (General)	Dosing	Manufacturing process	(b) (4) PMC to confirm that the lower action limit for fill weight supports withdraw of 8 mL label claim
Osmolality (General)	Patient Discomfort	DS manufacture since there are no additional	(b) (4)

		formulation during DP manufacture	(b) (4)
Protein Quantity (General)	Efficacy	DS and DP Manufacturing processes	
PS80	Product Stability	(b) (4) - May be impacted by steps in the DP manufacturing process	
Moisture Content (General)	Safety and stability (high levels may increase rate of degradation)	DP manufacturing process (lyophilization) and storage	
Reconstitution time (General)	product quality	-DP manufacturing process (lyophilization process) -May be impacted by storage	

a. Potency and Strength

Ebanga is supplied as a 400 mg single-dose sterile lyophilized powder in a (b) (4) glass vial, which provides a 50 mg/mL solution upon reconstitution. The potency of Ebanga is determined using the same ELISA binding assay as the one used for drug substance. Refer to the drug substance section for description of the potency assay.

b. Summary of Product Design

Ebanga is supplied as a sterile preservative-free, off-white to white lyophilized powder in a 20 mL (b) (4) glass vial containing 400 mg per vial. Upon reconstitution with 7.7 mL water for injection, the drug product contains 8 mL of a clear, colorless to slightly yellow solution containing 50 mg/mL ansuvimab, 20 mM histidine/histidine HCl, 240 mM sucrose, 0.02% polysorbate 80 at pH 6.0. The reconstituted drug product is further diluted in 0.9% sodium chloride or Lactated Ringer's solution for administration by intravenous infusion.

c. List of Excipients

Excipients in Ebanga DP include L-histidine (12.4 mg mg), L-histidine hydrochloride (b) (4) (16.8 mg) , Sucrose (657 mg), Polysorbate 80 (1.6 mg), and sterile water for injection USP (used for reconstitution).

d. Reference Materials

The same reference standards are used for DS and DP testing. Refer to the DS section above.

e. Manufacturing process summary

(b) (4)

Therefore, the DP commercial manufacturing process is adequately controlled.

f. Container closure

The DP primary container closure system includes a clear, 20 mL (b) (4) glass vial sealed with a 20 mm (b) (4) stopper and aluminum seal. Secondary packaging includes 36 vials of Ebanga packaged into a multiple-dose Carton with a 6 x 6 divider (36 wells), a single Package Insert leaflet and a single Dear Healthcare Professional (HCP) Letter.

g. Dating period and storage conditions

The dating period for drug product is 12 months at 2-8°C protected from light.

h. List of co-package components, if applicable: None

D. **Novel Approaches/Precedents:**

- Ebanga will be included in the U.S. Strategic National Stockpile (SNS). At this time, Ridgeback will provide one lot of Ebanga (lot # 037C20) to the SNS and requested exception from the 21 CFR 610.68 labeling requirements for the expiration date and exception from Section 582 (a)(3)(A)(i) of the FD&C act requirement for the linear and 2-dimensional data matrix barcode to appear on the vial label and 36-vial carton of the Ebanga lots stored at the SNS. The exception is requested for 5 years from the approval date. Lot-specific expiry information and regulatory actions will be available at a secure-access product specific website accessible using a quick response (QR) code printed on the vial label, 36-vial carton, and package insert. The expiration date and the linear and 2-dimensional data matrix will be included on the box that contains 1, 4, or 8- 36-vial cartons, which will serve as inventory management at the SNS. Ridgeback provided a relabeling plan and a post-approval shelf life extension protocol to support the exception.

  Per 21 CFR 610.68, the exception is allowable for the vial but not the 36-vial carton because the expiration date on the package label is a statutory requirement, section 351(a)(1)(B)(iii) (42 U.S.C. 262(a)(1)(B)(iii)), and therefore not subject to a waiver under 21 CFR 610.68. However, the Agency does not plan to take regulatory action for not labeling the 36-vial carton with the expiration date for product stored at SNS. (b) (4)

(b) (4), (b) (5)
. Refer to the approval letter of Ebanga for the final decisions made regarding this request.

- Compatibility of Ebanga with the administration conditions and materials in the labeling is based on a combination of compatibility studies, the conditions used during clinical studies, and safety risk assessments because the available compatibility studies are not sufficient to support the necessary in-use conditions and the in-use flexibility needed in an emergency or pandemic. For example, use of 5% dextrose as a diluent and a syringe pump are preferred over saline and IV bags for administration of small volumes to neonates. However there are no studies to support these in-use conditions. The Applicant agreed to a PMC to conduct comprehensive compatibility studies that support the preparation, handling, dilutions, and administration conditions indicated in the labeling as well as use of 5% dextrose for neonates. It is reasonable to conduct additional compatibility studies post-approval because in the case of an Ebola outbreak, the benefit of treatment surpasses the completion of additional compatibility studies.

E. **Any Special Product Quality Labeling Recommendations:**

- Store at 2°C to 8°C (36°F to 46°F) in original carton until reconstitution to protect from light. Do not freeze or shake. Unreconstituted vials may be kept at ambient temperature (15°C to 27°C [59°F to 81°F]) for NMT 24 h.
- Prior to use, allow vials to reach ambient temperature, reconstitute each 400 mg vial with 7.7 mL sterile WFI then dilute in 0.9% sodium chloride Injection or Lactated Ringer's solution per instructions in Table 1 of the label.
- Due to absence of microbial challenge studies, storage of reconstituted and diluted products is limited to a total of 4 hours at 2°C to 8°C or ambient temperature. Protect reconstituted and diluted product from light, and do not freeze or shake.
- Due to concerns with endotoxin levels, the diluent volumes for smaller patients were reduced as indicated in Table 1 of the label in order to meet the USP endotoxin safety limit and maintain the 1 hour infusion time.
- The expiration date for the product is available via a product-specific website.
- See comment on additional compatibility studies needed to support labeling in Section D above.

F. Establishment Information

OVERALL RECOMMENDATION: Approve			
Drug Substance and Drug Product			
Function	Site Information	DUN/FEI Number	Final Recommendation
-Drug substance and drug product manufacture and bulk packaging -Release and Stability testing -Cell bank storage	(b) (4)		CBI[1]: Approve - Based on 704 document review SVL[2]: Approve - Based on PLI

MCB and WCB secondary storage site	(b) (4)	Acceptable - No evaluation necessary
- MCB, WCB and EPC testing; (b) (4)		Approve -Based on previous history
MCB, and WCB (b) (4) testing (b) (4)		Acceptable – No evaluation necessary
Labeling, Secondary packaging, Drug product storage		Approve - Based on previous history

[1] CBI: biotechnology-derived API (sterile and non-sterile); [2]SVL: small volume parenteral, lyophilized

G. Facilities

All GMP facilities associated with the manufacture of Ebanga DS and DP are acceptable from a facilities assessment standpoint.

(b) (4)

Drug Product Manufacture

(b) (4)

(b) (4)

The inspection outcome was classified as VAI.

Therefore, the facility is acceptable for the proposed DP manufacturing operations based on the satisfactory outcome of the PLI.

Drug Substance Manufacture

(b) (4)

(b) (4)

(b) (4) The inspectional outcome was classified as VAI.

The facility is acceptable for the proposed DS manufacturing operations based on the satisfactory outcome of 704(a)(4) records review, currently acceptable CGMP compliance status and the recent relevant inspectional coverage.

Other facilities: The CGMP compliance status of the additional testing, storage, packaging and labeling sites is acceptable.

H. Lifecycle Knowledge Management

a. Drug Substance:

i. Protocols approved:
1. Concurrent process validation/lot release protocol: The upstream and downstream process validation protocols (b) (4) are approved with the appended change control amendment(s) that include (b) (4) in the protocols to be consistent with the parameters in Section 3.2.S.2.4 of the BLA.
2. Annual post-approval stability protocol
3. Protocols for extension of drug substance shelf-life
4. Protocols for qualification of new primary and working reference standards
5. Protocols for requalification/stability testing of the current and future reference standards
6. Protocols for concurrent validation of (b) (4)

ii. Outstanding review issues/residual risk: See Post Marketing Commitments in Section 1B III

iii. Future inspection points to consider:
1. See 704 review
2. Review analyst training records for the ELISA potency assay used for DS and DP release and stability testing
3. Review of all assay qualification and validation reports submitted to the BLA and confirm adequacy of the validation exercise for the icIEF, CE-SDS non-reduced, and N Glycan analysis methods used for DS and DP release and/or stability testing

b. Drug Product

i. Protocols approved:

1. Annual post-approval stability protocol
2. Protocol for extension of drug product expiry
3. Final DP shipping qualification protocol

ii. Outstanding review issues/residual risk: See Post Marketing Commitments in Section 1B III

iii. Future inspection points to consider: See comments above related to analytical method performance

---

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

/s/

FRANCES NAMUSWE
12/16/2020 08:30:43 PM

MARIA T GUTIERREZ LUGO
12/16/2020 08:54:23 PM

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	December 16, 2020
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Davinna Ligons, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 3
Application:	BLA 761172
Applicant:	Ridgeback Biotherapeutics, LP
Submission Date:	May 29, 2020
Product:	Ebanga (ansuvimab-zykl)
Dosage form(s):	For injection
Strength and Container-Closure:	400 mg as a lyophilized powder in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information, container labels, and carton labeling (submitted on December 15, 2020) are acceptable from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

Ebanga is under development for stockpiling in the U.S. Strategic National Stockpile (SNS) with expected limited distribution unless a public health emergency arises in response to an Ebola outbreak. Ridgeback Biotherapeutics, LP proposed an exception from the labeling requirement to include an expiration date on the vial label (container) per §610.60(a)(4) and 36-vial primary carton labeling per §610.61(d). Exceptions to labeling are requested and granted under 21 CFR 610.68(f) and can be permissible by the CDER Center Director for the container label, however, the expiration date on the package label, a requirement of 21 CFR 610.61(d), is a statutory requirement of the PHS Act and not subject to a waiver under 21 CFR 610.68. OBP Labeling assessed the description of the packaging configuration provided in the labeling exception grant letter as related to the labeling exception request for the expiration date and determined that the description of the packaging configuration is consistent with the packaging configuration described in section 16 of the prescribing information.

Ridgeback Biotherapeutics, LP proposed to exclude a linear and 2-dimensional (2D) data matrix barcodes on the vial label (container) and 36-vial primary carton labeling per §610.67 and to include a linear and 2-dimensional (2D) data matrix barcodes on the boxes containing 1, 4, or 8 36-vial cartons. OBP Labeling deferred the grant for a waiver from serialization requirements on the vial label and primary 36-vial carton labeling per the Drug Supply Chain Security Act (DSCSA) to CDER/OC/ODSIR/DSCI/SCSPB. ODSIR oversees the implementation/enforcement of the DSCSA, a law that requires, among other things, that manufacturers put a product identifier (a 2D data matrix barcode with statutorily-specified information) on certain levels of drug packaging.

Ridgeback Biotherapeutics, LP proposed to include a QR code on the vial label, carton labeling, and prescribing information that will land the user on the Ebanga website. The website (www.EBANGA.co), also printed on all labeling, is intended to provide access to lot-specific information including the expiration dating period for the specific lot granted labeling exception of the expiration date. QR code is a type of 2-dimensional barcode that is not the same as a 2D data matrix barcode and does not encode the same type of required information. OBP Labeling deferred the use of a QR code in labeling to CDER/OMP/OPDP/DAPRI. In an email dated October 27, 2020, OPDP/DAPRI indicated that they do not have any concerns with replacement of the expiration date with a QR code, from a promotional standpoint.

CONCLUSION

The prescribing information, container labels, and carton labeling (submitted on December 15, 2020) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

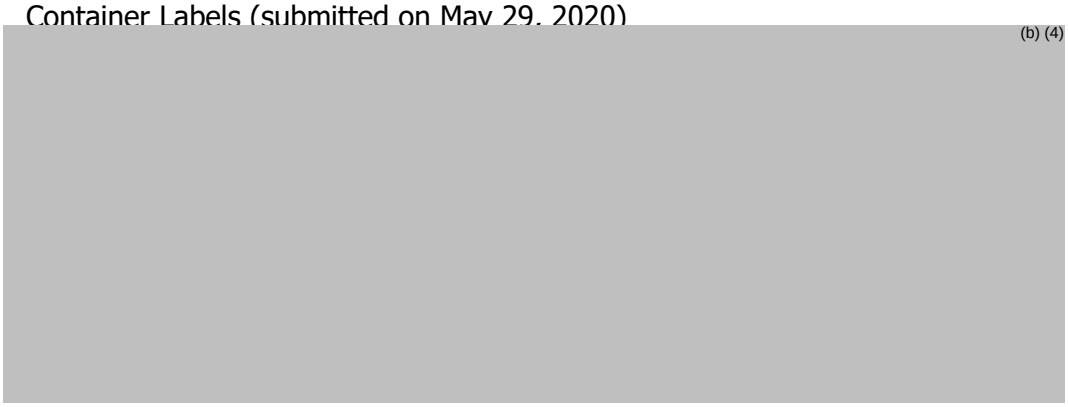
APPENDICES

Appendix A: Proposed Labeling

Prescribing Information/Instructions for Use (submitted on June 9, 2020 \\cdsesub1\evsprod\bla761172\0009\m1\us\114-labeling\draft\labeling\draft-labeling-text-word-version.docx)

Container Labels (submitted on May 29, 2020)

(b) (4)



1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise from "Mfd (b) (4)" to the qualifying phrase for the manufacturer, the city that is listed on FDA form 356h, and include a placeholder for the US license number as follows: "Mfd by: Ridgeback Biotherapeutics, LP (b) (4) U.S. License No. xxxx"
The Applicant acceptably revised the format as requested and with an updated address listed on Form FDA 356h (Ridgeback Biotherapeutics, L.P., (b) (4) Miami, FL 33133 USA) per the change of address submission dated November 16, 2020.

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the strength presentation from (b) (4) to the correct presentation for dry solids as "400 mg/vial" or "400 mg per vial"
The Applicant acceptably revised to "400 mg per vial"

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials.
Applicant's response: The Sponsor confirms that there is no text on the ferrule and cap overseal of the vials.

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located *Applicant's response: Ridgeback confirms that a sufficient area of the container will remain uncovered subsequent to application of the container label, such that visual inspection of the full length or circumference of the vial is allowable.*

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

NDC numbers **(container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The Applicant requested an expiration date exemption for the vial label
The Agency determined this to be acceptable

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise from "(b) (4)" to Dosage: See prescribing information to align with terminology for PLR formatted labeling.
The Applicant revised to "Recommended Dosage: See prescribing information."

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise from "Mfd (b) (4)" to the qualifying phrase for the manufacturer, the city that is listed on FDA form 356h, and include a placeholder for the US license number as follows: "Mfd by: Ridgeback Biotherapeutics, (b) (4) FL (b) (4) U.S. License No. xxxx"
The Applicant acceptably revised the format as requested and with an updated address listed on Form FDA 356h (Ridgeback Biotherapeutics, L.P., (b) (4) Miami, FL 33133 USA) per the change of address submission dated November 16, 2020.

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Provide the number of containers per carton, e.g.,
Contents: thirty-six 400 mg vials
Note: There are three (3) scaled secondary cartons that fit either one (1), four (4) or eight (8) primary cartons. The scaled secondary cartons contain the expiry date and the linear and 2-dimensional data matrix barcodes
The Applicant revised to "Contents: 36 x 400 mg vials" etc

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the strength presentation from (b) (4) to the correct presentation for dry solids as "400 mg/vial" or "400 mg per vial" and relocate to appear after the dosage form on the principal display panel as follows:

Proprietary name
(proper name-xxxx)
For injection
400 mg per vial
For Intravenous (b) (4)

The Applicant revised as requested but with "For intravenous use"

(b) (4)

The Applicant deleted as requested

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Consider revising storage statement to read as follows: "**REFRIGERATE**: Store 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 (b) (4) 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.
The Applicant revised as requested

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: *see comment above strength presentation and route of administration appearing with the name and dosage form on the PDP*

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise (b) (4)" to read as follows: "Each single-dose vial delivers 400 mg of ansuvimab-xxxx, and L-histidine (12.4 mg), L-histidine HCl (16.8 mg), polysorbate 80 (1.6 mg), and sucrose (657 mg).
The Applicant revised as requested

Add "Reconstitution with 7.7 mL of Sterile Water for Injection, USP yields a solution containing 50 mg/mL of ansuvimab-xxxx that delivers 8 mL, at an approximate pH of 6."
The Applicant revised as requested

Add post reconstitution storage information: "Reconstituted solution in the vials may be kept at ambient temperature (15°C to 27°C [59°F to 81°F]) or stored refrigerated at 2°C to 8°C (36°F to 46°F), protected from light, for up to four (4) hours. This 4-hour window includes time required for further dilution and EBANGA solution should be infused immediately upon further dilution."
The Applicant revised as requested

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The Applicant requested an expiration date exemption for the vial label and 36-vial primary carton labeling
See exception request grant letter

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Consider revising the treatment of dosage from "(b) (4) " to read as follows: "Dosage: See Prescribing Information"
The Applicant revised as requested

Dispensing container (package labeling)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The dosage form for dry solids and lyophilized powders is "for injection". "(b) (4) " has been removed.
The Applicant revised as requested

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The dosage form for dry solids and lyophilized powders is "for injection". *The Applicant revised as requested*

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted drug; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes); confirm product's incompatibilities, and ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Relocated preparation and administration information in (b) (4) to section 2. *The Applicant revised as requested*

Added "20 minutes" as the time that it will take to reach ambient temperature once removed from refrigerated ["Prior to reconstitution, allow EBANGA vial(s) to reach ambient

temperature [redacted] (b) (4) for approximately 20 minutes"]. *The Applicant accepted the revision*

Added "this 4-hour window includes time required for further dilution and EBANGA solution should be infused immediately upon further dilution." *The Applicant accepted the revision*.

Revised paragraph that describes storage requirements for diluted infusion solution to indicate that the storage time includes the reconstitution time. Added "These time limits include reconstitution times". *The Applicant accepted the revision.*

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised to standard format for dosage form.
The Applicant revised as requested

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Deleted the tradename placeholder form this 1st paragraph since this paragraph discusses the drug substance. *The Applicant revised as requested*

Request to provide the molecular weight. *The Applicant provided a molecular weight of 147 kDa.*

Added the ingredient paragraph as follows:
Each single-dose vial delivers 400 mg of ansuvimab-xxxx, and L-histidine (12.4 mg), L-histidine HCl (16.8 mg), polysorbate 80 (1.6 mg), and sucrose (657 mg). *The Applicant revised as requested*

(b) (4)

OBP labeling response: This sentence is intended to provide the concentration of the reconstituted solution as 50 mg/mL and the volume that can be withdrawn (deliverable volume) from the vial to prepare and administer the dose. A similar sentence is provided in section 2 and reiterated here for consistency. (b) (4) *Revised to previous recommended language and awaiting your response for extractable volume data. The Applicant revised as requested "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."*

Full Prescribing Information	
15 & 16 Cytotoxic Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16: xxxx is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The dosage form has been added. *The Applicant revised as requested*

Terms sterile and preservative free have been added. *The Applicant revised as requested*

(b) (4) has been added. *The applicant revised to include various 36 count carton configuration packs. OBP labeling requested further packaging configuration clarification as "Confirm if the packaging configuration includes one vial per primary carton and 36 primary cartons per outer carton?". The Applicant confirmed that 36 vials are placed in a paperboard carton with a 6X6 chipboard divider. There are three (3) scaled secondary cartons (reusable insulated shipper) that fit either one (1), four (4) or eight (8) primary cartons. The scaled secondary cartons contain the expiry date and the linear and 2-dimensional data matrix barcodes.*
OBP Labeling revised to "EBANGA (ansuvimab-zykl) for injection is supplied as a sterile, preservative-free, off-white to white lyophilized powder in a single-dose vial (NDC 80673-001-001) for reconstitution and further dilution.

One primary carton (NDC 80673-001-036) contains thirty-six 400 mg vials packaged in a (b) (4) *box containing either one primary carton (NDC 80673-777-01), four primary cartons (NDC 80673-777-04), or eight primary cartons (NDC 80673-777-08)." The Applicant accepted the revision.*

(b) (4) has been revised to "handling". *The Applicant accepted the revision.*

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The qualifying phrase to use for the manufacturer (applicant on FDA for 356h) is "manufactured by" and the qualifying phrase can be provided as "Manufactured and distributed by" to show that Ridgeback Biotherapeutics, LP is also considered to be the distributor. *The Applicant revised to "Manufactured by"*

The placeholder for the US license number has been added. *The Applicant accepted the revision*

Medication Guide Evaluation (N/A)
Patient Information Labeling Evaluation (N/A)
Instructions for Use Evaluation (N/A)

7 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 12/16/2020 12:55:10PM
GUID: 50814c7000007a3d59329f660d8ddf02

Davinna Ligons

Digitally signed by Davinna Ligons
Date: 12/16/2020 02:30:03PM
GUID: 5822293b004ccdbf2f2e504746be3f82

Memorandum of Review for Immunogenicity Assays

Original BLA: 761172

Primary reviewer: Davinna L. Ligons, Ph.D.
Secondary Reviewer: Frances Namuswe, Ph.D.

Product: Ansuvimab

Indication: Treat patients with Ebola infection

Route of Admin: Intravenous
Dose Regimen: 50 mg/kg

Sponsor: Ridgeback Biotheraupetics, LP
Clinical Division: Division of Antivirals (DAV)

Received Date: May 29, 2020 (final submission – rolling BLA)
Target Date: November 25, 2020
PDUFA Date: January 29, 2021

Immunogenicity Executive Summary and Recommendation

Ansuvimab is a recombinant human IgG1 monoclonal antibody directed to the Ebola Virus glycan cap and core domains of the glycoprotein (GP1) subunit, leading to neutralization of the virus. Ansuvimab also exhibits antibody-dependent cellular cytotoxicity (ADCC) activity against cells expressing the Ebola glycoprotein in vitro. Ansuvimab is intended for the treatment of Zaire ebolavirus infection. Drug Substance (DS) and Drug product (DP) are manufactured at (b) (4) DP is a lyophilized powder with strength of 400 mg per vial and is administered as single intravenous dose of 50 mg/kg diluted in diluent.

Recommendation: From an immunogenicity assay perspective, this BLA is recommended for approval despite suboptimal validation of the ADA assay. Specifically, the cut point was inadequately determined, the assay shows poor specificity, drug tolerance and assay selectivity were not assessed and available data suggest potential matrix and drug interference in the assay, and high and low positive controls needed for monitoring the sensitivity of the assay and Hook effect, respectively, during routine runs were not included in the assessment of the clinical samples. However, based on discussions with the clinical pharmacology review team, we do not recommend repeating the validation exercise at this time because: 1) immunogenicity was

only assessed in healthy volunteers but not assessed in the patients with Ebola. In healthy volunteers, two baseline samples screened positive and ADAs were not detected post-treatment. However, the ADA results in healthy volunteers may not inform the incidence of ADAs in patients with Ebola; 2) ansuvimab demonstrated a favorable impact in the treatment of Ebola. This outcome outweighs the possible impact of ADAs on safety and efficacy; 3) the Ebola virus is an exogenous target; therefore, off-target effect of ADAs is unlikely; 4) ansuvimab is an IgG1 monoclonal antibody administered as a single dose; therefore, the ADA rate is likely to be low; and 5) a multidose clinical study is not requested by the Agency. Thus, a validated ADA assay is not needed at this time because samples from Ebola positive patients treated with ansuvimab are not available. Since the accuracy of the immunogenicity results in healthy volunteers cannot be verified, it is recommended that immunogenicity data are not reported in section 6.2 of the labeling.

The applicant was advised that if future clinical studies are needed and ADA levels need to be assessed as part of those studies (e.g. multidose studies), a validated immunogenicity assay will need to be implemented.

Review

Documents Reviewed	Submission Date
Doc 1772 - Qualification of Anti-Drug Assay in the Detection of Anti-MB114- MAB Using (b) (4) Assay Platform	5/29/2020
Doc 1792 - Report for Qualification of the Anti-Drug Assay in the Detection of Anti-MB114 Antibodies	5/29/2020
SOP 5515 Anti-Drug Assay (ADA) using (b) (4) Assay Platform (ADA) Using (b) (4) Assay Platform	5/29/2020
18-i-0069 – Clinical study report (Phase 1)	5/29/2020
IR response	9/29/2020
IR response	11/6/2020

Validation of Anti-Drug Antibody Assay

Method Principle

The ADA assay was developed by (b) (4) and conducted at the Vaccine Immunology Program (VIP). SOP 5515 Anti-Drug Assay (ADA) using (b) (4) Assay Platform describes the procedure of the ADA assay used during validation and testing of clinical samples. (b) (4)

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

ADA Assay Assessment	**Not demonstrated to be suitable for its intended purpose**	*Overall, the ADA assay was not adequately validated*

Additional Assessor Comments:

- *Method validation is inadequate to demonstrate that the ADA assay is fit for its intended purpose due to suboptimal determination of the cut point, absence of drug tolerance and selectivity data, and poor specificity. However, for the reasons summarized above, a PMC for re-validating the assay was not issued.*

- *In an IR dated 12/3/2020, the Sponsor was informed that if assessment of immunogenicity is to be included in any future clinical studies and/or if revisions to section 6.2 of the labeling are to be made to include clinical immunogenicity data, fully validated anti-drug antibody (ADA) assays will be needed. The Sponsor was informed that the assays should be validated in accordance with the January 2019 guidance for industry: Immunogenicity Testing of Therapeutic Protein Products - Developing and Validating Assays for Anti-Drug Antibody Detection and should include screening, confirmatory, and titer assays. If necessary, the Sponsor should develop a neutralizing ADA assay to further characterize ADA responses. Furthermore, the ADA assays should be confirmed fit for testing Ebola positive patient samples prior to assessing immunogenicity in the clinical samples. In addition to confirming the cut point in the target population, the Sponsor was advised that assay parameters e.g. specificity, selectivity, minimal required dilution, etc be additionally validated using treatment naïve Ebola positive patient samples because the sample matrix in this population may be different from normal serum and may impact assay results. In accordance with 21 CFR 601.12, the Sponsor may update section 6.2 of the labeling with the immunogenicity data generated with adequately validated ADA assays.*

Immunogenicity testing in phase 1 clinical samples

Method

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Assessor comments:

Due to inadequate validation of the ADA assay, the data generated with the clinical samples are not reliable. Considering that a single dose of ansuvimab was administered, it is likely that the ADA rate was low and the two baseline samples that tested positive are false positives because according to the Sponsor the healthy volunteers had no prior exposure to ansuvimab.

In the IR response dated 11/6/2020, the Sponsor indicated that the clinical runs were conducted without a positive control and that only a negative control run in quadruplicate was included the clinical runs. The average ECL value of the negative control was used to determine the cut point of the plate. The Sponsor indicates that the assay suitability criteria of %CV ≤ (b) (4) *for each sample ran in quadruplicate were met and no samples were retested. However, data for all the suitability criteria indicated in the SOP were not provided as requested in the IR and thus, it is not clear whether outliers were removed. Generally, it is not acceptable to run clinical samples without a positive control to ensure the assay is performing as validated. The assessment of the clinical samples is suboptimal.*

Davinna Ligons

Digitally signed by Davinna Ligons
Date: 12/16/2020 09:51:33AM
GUID: 5822293b004ccdbf2f2e504746be3f82

Frances Namuswe

Digitally signed by Frances Namuswe
Date: 12/16/2020 09:53:34AM
GUID: 5114480100018b1165eee57166b2f771