Summary Basis for Regulatory Action

Date:	July 20, 2023
From:	Taruna Khurana, PhD Review Committee Chair Division of Vaccines and Related Products Applications Office of Vaccines Research and Review
BLA STN:	125761/0
Applicant:	Emergent Product Development Gaithersburg Inc.
Submission Receipt Date:	Rolling Submission: December 14, 2021, and April 20, 2022
Action Due Date:	July 20, 2023
Proper Name:	Anthrax Vaccine Adsorbed, Adjuvanted
Proprietary Name:	CYFENDUS
Indication:	For post-exposure prophylaxis of disease following suspected or confirmed exposure to *Bacillus anthracis* in persons 18 through 65 years of age when administered in conjunction with recommended antibacterial drugs

Recommended Action: The Review Committee recommends approval of this product.

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Director, Product Office

Discipline Reviews	Reviewer / Consultant
CMC	
• CMC Product (OVRR/DBPAP)	Tod Merkel, PhD Anita Verma, PhD
• CMC Adjuvant (OVRR/DVP)	Marina Zaitseva, PhD
• Facilities review (OCBQ/DMPQ)	Kathleen Jones, PhD Jared Greenleaf Neetu Dahiya, PhD
• QC, Test Methods, Product Quality (OCBQ/DBSQC)	Kouassi Ayikoe, PhD Marie Anderson, PhD Ritu Agarwal, PhD Seth Schulte, MS Wei Tu, MD
Clinical	
• Clinical (OVRR/DVRPA) • Postmarketing safety epidemiological review (OBPV/DE) • BIMO (OCBQ/DIS)	Alexandra Worobec, MD Jane Woo, MD Haecin Chun, MS
Statistical	
• Clinical data (OBPV/DB/VEB)	Ye Yang, PhD
Non-clinical/Pharmacology/Toxicology	
• Toxicology (OVRR/DVRPA) • Developmental toxicology (OVRR/DVRPA) • Animal pharmacology (OVRR/DBPAP)	Claudia Wrzesinski DVM, PhD Claudia Wrzesinski DVM, PhD Tod Merkel, PhD
Clinical Pharmacology	
Labeling	
• Promotional (OCBQ/DCM/APLB) • Proprietary Name Review (OCBQ/DCM/APLB) • Carton & Container (OVRR/DVRPA)	Oluchi Elekwachi, PharmD, MPH Oluchi Elekwachi, PharmD, MPH Daphne Stewart
Other Reviews not captured above categories: • Consult-Clinical data standardization (OVRR/DVRPA) • Consult-DSCSA Exemption (OCBQ) • Consult-Pharmacology Study (CDER/OTS/OCP/DIDP) • CMC Regulatory Coordinators (OVRR/DBPAP)	 Brenda Baldwin, PhD Linda Silvers, DVM, MPH Xiaohui Wei, PhD Leslie Wagner, BS Roger Plaut, PhD

• Regulatory Project Manager (OVRR/DVRPA) • Regulatory Project Manager (OCBQ/DMPQ/ARB)	Diana Oram, PhD Iryna Zubkova, PhD
Advisory Committee Summary	NA

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1. Introduction

Emergent Product Development Gaithersburg Inc. (also referred to as the applicant or Emergent in this document) submitted an original Biologics License Application (BLA), STN 125761 to the United States Food and Drug Administration (FDA) for licensure of Anthrax Vaccine Adsorbed, Adjuvanted. STN 125761/0 was a rolling application, where the submission was initiated on December 14, 2021, and the final part was submitted on April 20, 2022. The applicant submitted an amendment that included revised clinical

datasets on September 9, 2022, and this amendment was designated a major amendment resulting in an action due date of July 20, 2023.

Anthrax Vaccine Adsorbed, Adjuvanted is the proper name, and the proprietary name is CYFENDUS. CYFENDUS is indicated for post-exposure prophylaxis of disease following suspected or confirmed exposure to *Bacillus anthracis* in persons 18 through 65 years of age when administered in conjunction with the recommended antibacterial regimen.

CYFENDUS consists of Anthrax Vaccine Adsorbed (AVA), which includes anthrax vaccine (AV) filtrate adsorbed to aluminum hydroxide (b) (4) , and the adjuvant CpG 7909. CYFENDUS is a sterile, milky white suspension supplied in a multiple dose clear glass vial closed with a multi-puncture rubber stopper and a flip top aluminum seal. Each vial is filled with (b) (4) mL of the final drug product (DP) solution. CYFENDUS is a two-dose vaccine for intramuscular (IM) administration at two-week intervals. A single dose of vaccine is 0.5 mL. The shelf life of CYFENDUS is 48 months from the date of manufacture when stored at 2°C to 8°C. The date of manufacture is defined as the date of addition of CpG 7909 to the bulk drug substance (DS) under sterile conditions.

BioThrax (also manufactured by the applicant) is the only licensed anthrax vaccine in the US (License #1755, BLA 103821). BioThrax is indicated for prevention of disease caused by *Bacillus anthracis* in persons 18 through 65 years of age. The vaccine is approved for pre-exposure prophylaxis of disease in persons at high risk of exposure and post-exposure prophylaxis (PEP) of disease following suspected or confirmed *B. anthracis* exposure, when administered in conjunction with recommended antibacterial drugs. BioThrax is administered subcutaneously (SC) as a three-dose series at Weeks 0, 2, and 4 for post exposure prophylaxis[1].

The Advisory Committee on Immunization Practices (ACIP) currently recommends a 60-day course of antibiotics (ciprofloxacin or doxycycline) in conjunction with three doses of BioThrax administered two weeks apart for PEP of anthrax[2].

Because of the rapid progression and fatal nature of inhalational anthrax, clinical trials to demonstrate effectiveness of a PEP anthrax vaccine are not feasible or ethical. Therefore, animal post-exposure survival data were used as the basis for demonstration of effectiveness of CYFENDUS for the proposed indication, under the Animal Rule, 21 CFR 601 Subpart H for Biologics, “Approval of Biological Products when Human Efficacy Studies are not Ethical or Feasible.” CYFENDUS clinical trials were conducted in accordance with the recommendations from the 2010 Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting[3] and were similar in design to those used to support the licensure of BioThrax for the PEP indication under supplement to BLA (sBLA) STN 103821/5344[4].

The applicant conducted animal efficacy studies in guinea pigs and non-human primates (NHP). The toxin neutralizing antibody (TNA) 50% neutralization factor (NF_{50}) levels and animal post challenge survival data from these studies support the PEP use of CYFENDUS.

Additionally, per the FDA recommendations, the target TNA NF_{50} threshold of 0.56, derived from the BioThrax rabbit PEP study, was used by the applicant as the basis for

the primary clinical immunogenicity endpoint in the Phase 3 study (Study EBS.AVA.212) for CYFENDUS.

The clinical data submitted to this BLA to support the safety and effectiveness of CYFENDUS for the PEP indication against anthrax in healthy adult subjects 18 through 65 years of age comprised four clinical studies: EBS.AVA.201, EBS.AVA. 208, EBSm.AVA.210, and EBA.AVA.212. Studies EBS.AVA.201 and 208 established the appropriate dose and dosing schedule of CYFENDUS. Phase 3 study EBS.AVA.212 was conducted to bridge human TNA NF_{50} levels to animal TNA NF_{50} level thresholds (≥0.56 in rabbit and ≥0.29 in NHP) that corresponded to 70% survival after inhalational anthrax challenge. Study EBS.AVA.210 evaluated the impact of CYFENDUS administration on the pharmacokinetics (PK) of ciprofloxacin or doxycycline and conversely, the effect of these two antimicrobial drugs on the immune response after vaccination with CYFENDUS. The study showed no clinically relevant effect of the vaccine on the PK profile of the antimicrobials, and administration of antimicrobials did not decrease the immunogenicity of CYFENDUS when dosed using the PEP schedule. All four clinical studies also evaluated safety in over 3000 healthy subjects for up to 12 months after administration of the last dose of the vaccine. The safety evaluation revealed no new safety signals, with most adverse events reported being mild to moderate local and systemic reactogenicity events.

This document summarizes the bases for standard approval of CYFENDUS based on Animal Rule immunogenicity and survival bridged to human immunogenicity data for the PEP indication in adults 18 through 65 years of age.

2. Background

Anthrax is caused by spores of the toxigenic, aerobic, Gram-positive, encapsulated bacterial species *B. anthracis*. The route of entry of spores determines the type of anthrax infection. There are four clinical types of anthrax resulting from infection: cutaneous, ingestion, injection, and inhalational. Cutaneous anthrax is the most reported infection (95% to 99%) and with antimicrobial treatment has a fatality rate of <2% while inhalational anthrax is the deadliest form of infection with a fatality rate of 67% to 88% even with antimicrobial treatment[5]. In inhalational anthrax, inhaled spores migrate to the lymph nodes where they germinate into vegetative bacilli. These bacilli produce and release toxins. The production of large quantities of anthrax toxins by bacilli play a critical role in disease symptomatology and progression, which can result in death.

Military personnel are immunized routinely with the currently licensed anthrax vaccine (BioThracx) as a precautionary measure to ensure health and well-being against potential *B. anthracis* exposure. While naturally occurring inhalation anthrax is rare in humans, the potential for use of *B. anthracis* as a bioweapon, due in part to the ease of production of aerosolized spores and the high case fatality rate, is a concern. Recognizing the importance of preparedness, the US government prioritized the development of countermeasures against anthrax, with a particular focus on developing an effective and easily administered anthrax vaccine for use following a mass exposure event.

Emergent initiated clinical and product development of Anthrax Vaccine Adsorbed, Adjuvanted under IND 14451 in 2010, and on August 19, 2021, the IND received orphan drug designation for the indication of "post-exposure prophylaxis of anthrax disease resulting from suspected or confirmed exposure to *Bacillus anthracis.*" The clinical and non-clinical investigational name of CYFENDUS is AV7909.

Over the course of development, the FDA had multiple communications and correspondences with the applicant. Table 1 provides a list of key regulatory activities associated with this BLA.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	March 01, 2010
2. IND submission	September 10, 2010
3. Fast Track designation granted	June 03, 2011
4. Orphan Drug designation granted	August 19, 2021
5. Pre-BLA meeting-CMC (written response only)	April 27, 2021
6. Pre-BLA meeting-Clinical and Non-clinical (written response only)	October 12, 2021
7. BLA 125761/0 submission (rolling submission)	December 14, 2021, and April 20, 2022
8. BLA filed	June 17, 2022
9. Mid-Cycle communication	Canceled upon applicant's request
10. Late-Cycle meeting	Canceled upon applicant's request
11. Major Amendment	September 23, 2022
12. Action Due Date	July 20, 2023

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Product Composition

CYFENDUS is supplied as a sterile suspension in 10 mL multidose glass vials, each containing 10 doses. Each 0.5 mL dose of the vaccine is formulated to contain AVA, which is the drug substance (DS) for CYFENDUS, and CpG 7909 adjuvant. The composition of CYFENDUS and the functions of the components are provided in Table 2.

Table 2: Composition of CYFENDUS

Component	Quantity per mL	Function
Total adsorbed AV filtrate	100 µg	Active ingredient
Aluminum Hydroxide (b) (4)	1.3 mg	Adjuvant
Sodium Chloride	8.5 mg	(b) (4)
Formaldehyde Solution, (b) (4)	100 µg	(b) (4) Preservative
Benzethonium Chloride	25 µg	Preservative
CpG 7909	0.5 mg	Adjuvant

Drug Substance (Anthrax Vaccine Adsorbed)

The DS is manufactured using (b) (4) process, ingredients, and concentrations as for BioThrax (Anthrax Vaccine Adsorbed; AVA). AVA is composed of anthrax vaccine filtrate (AV) adsorbed to aluminum hydroxide. The (b) (4)

Manufacturing Overview:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

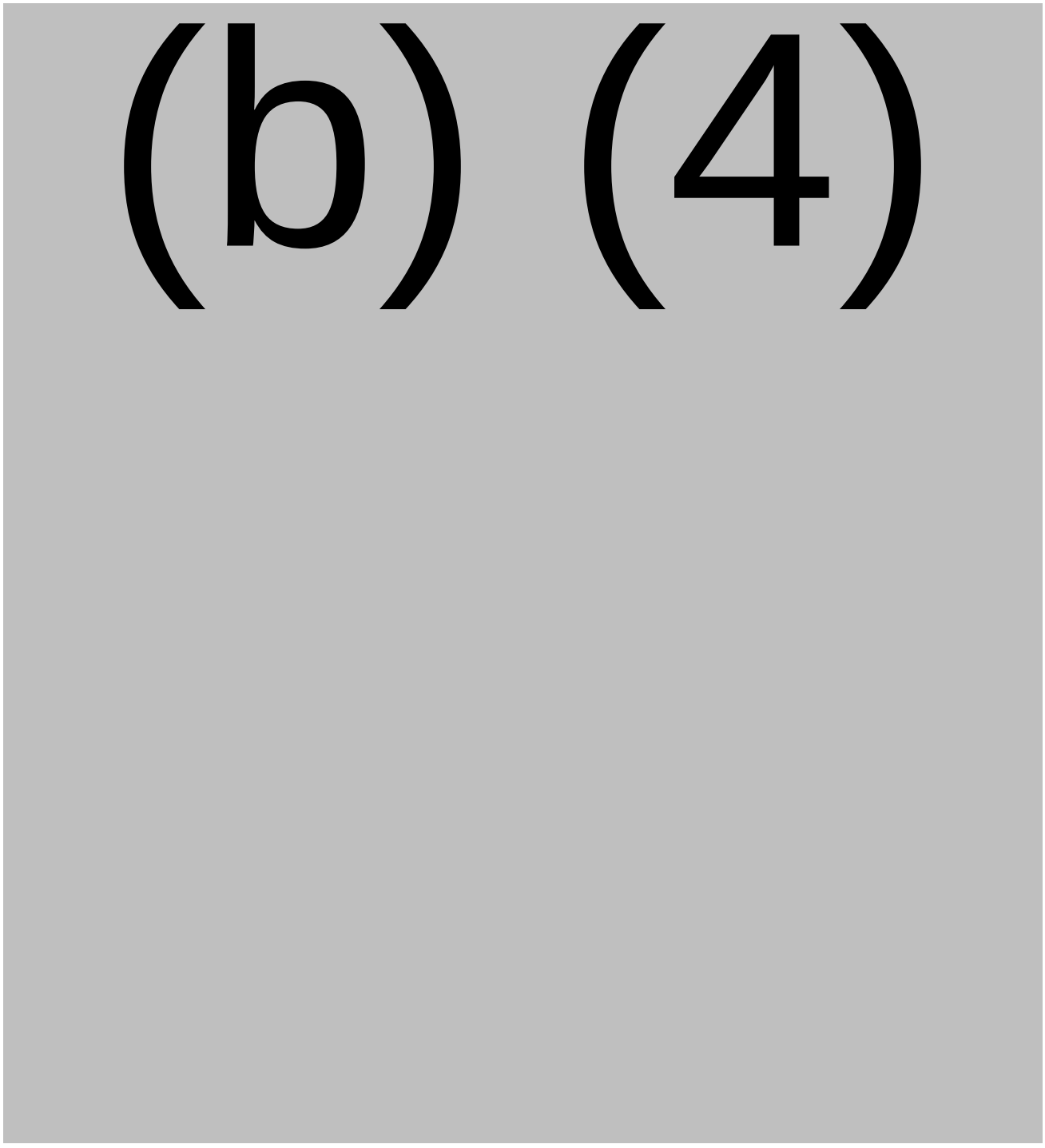
Drug Substance (CpG 7909)

CpG 7909 is used as an adjuvant in this vaccine. CpG 7909 is a synthetic DNA molecule of 24 nucleotides in length with a molecular weight of (b) (4) Daltons. This adjuvant acts as a TLR-9 agonist. The applicant has cross referenced a type V Drug Master File (b) (4)

(b) (4) for detailed information for adjuvant manufacturing, quality control, in-process testing, stability, storage, and distribution.

Manufacturing Overview:

(b) (4)



(b) (4)

Drug Product

CYFENDUS is a sterile, milky white suspension supplied in a clear borosilicate multi-dose container with a multi-puncture rubber stopper and a flip top aluminum seal. Each vial contains 10 doses of the vaccine, with each dose being 0.5 mL.

Manufacturing Overview:

The DP, composed of AVA plus CpG 7909 adjuvant, is filled into a 10 mL multiple dose clear glass vial. The current commercial manufacturing process has the following main steps.

(b) (4)

(b) (4) Final filled vials are shipped to EBOL for 100% visual inspection, labeling, packaging, and release testing. The vials are stored at 2°C to 8°C until release.

(b) (4) Shipping of the product from EBOL is conducted using qualified shippers and a validated procedure. The shipment process is conducted (b) (4)

Process Validation:

The DP PPQ studies were performed using (b) (4)

The PPQ studies for the formulation and fill of the DP are satisfactory. CBER considers the DP manufacturing process consistent and validated.

DP Specifications:

DP specifications for release are included in Table 5.

Table 5: Drug Product Release Specification

Test Parameter	Test Method	Specification
Appearance	Visual Inspection	Milky white suspension
Detection of Protective Antigen (PA)	(b) (4)	(b) (4)
(b) (4) CpG 7909		
(b) (4) CpG 7909		
Aluminum content		
Formaldehyde content		
Sodium Chloride content		
Benzethonium Chloride content		
Sterility		
Relative Potency		
(b) (4)		

Stability:

(b) (4) DP lots were placed in the primary stability program for testing at the real-time (2°C to 8°C) and accelerated (b) (4) storage conditions. Real-time stability data for 48 months are available for (b) (4) lots (Lots (b) (4) . The rest of the lots currently have stability data ranging from 24 to 33 months. The additional stability studies include testing under maximum (b) (4) during the DP manufacturing process, in-use, and long-term storage in an upright orientation. The applicant also tested selected lots for (b) (4)

The stability data generated from the (b) (4) primary lots support a 48-month shelf life for CYFENDUS when stored at 2°C to 8°C in the final container closure system. The date of manufacture is defined as the date of addition of CpG 7909 to the bulk DS under sterile conditions.

The analytical methods used in the stability program are the same as those used for final DP release testing, with Container Closure Integrity and Antimicrobial Effectiveness as additional tests.

The applicant will complete all ongoing stability studies and place one lot of CYFENDUS on stability testing every year. The applicant's commitment and post approval stability plan are acceptable.

Serology assay and assay used to measure relative potency of CYFENDUS

Toxin Neutralizing Antibody (TNA) Assay

The TNA assay was used as a serology assay for assessing circulating neutralizing antibody levels in nonclinical and clinical studies (EBS.AVA.201, EBS.AVA.208, EBS.AVA.210, and EBS.AVA.212). The assay quantifies the functional antibody titers in serum that (b) (4) cell line. The applicant employed two animal models for animal efficacy studies: guinea pigs and NHP. To assess the effectiveness of the proposed human dose of AV7909, immune responses associated with survival post-challenge in guinea pigs and NHP were bridged to human immunogenicity data to infer clinical benefit. Because the TNA assay is species-independent, it can be used for direct comparison of functional immune response across species, thereby providing a mechanism for bridging animal and human immunogenicity data to support licensure of CYFENDUS under the Animal Rule. The high throughput version (htpTNA) of the TNA assay developed and validated at (b) (4) was used for antibody analysis of clinical serology. This version of the assay is based on one originally validated by the Centers for Disease Control and Prevention[6]. The functional antibody titer data demonstrate adequate performance of the htpTNA as a serology assay to support CYFENDUS PEP licensure and provide evidence that it is suitable for its intended use.

(b) (4) **assay**

The (b) (4) assay serves as the release and stability assay to report the relative potency (RP) of the DP. This is an (b) (4) test, which determines the RP of the DP by comparing test lots to a qualified reference vaccine lot of known potency. In this assay, groups of (b) (4)

The (b) (4) assay was appropriately validated for linearity, precision, and accuracy. The assay met all validation acceptance criteria. Based on release data of (b) (4) DP lots (supplied to the SNS under pre-Emergency Use Authorization (EUA)) collected using (b) (4) as a reference vaccine, an offset value of (b) (4) for setting acceptance criteria. The applicant proposed acceptance criteria for the DP release and stability specifications as (b) (4) RP respectively. In the BLA, the applicant committed that release and stability acceptance criteria will be reassessed once data from at least (b) (4) lots of the DP are generated after the implementation of (b) (4) as the reference vaccine. This was agreed upon during the pre-BLA meeting. (b) (5) as indicated in the inspectional follow-up memo dated June 03, 2023.

b. Testing Specifications

The analytical methods and their validations and/or qualifications for the CYFENDUS vaccine (b) (4) DP were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of CYFENDUS, are listed in table below. The activities performed and the inspectional histories are noted in Table 6.

Table 6 Facilities involved in manufacturing and release testing of CYFENDUS

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
Emergent BioDefense Operations Lansing LLC 3500 N Martin Luther King Jr Blvd Lansing, MI 48906 *DS manufacturing; Bulk DP manufacturing; DP release testing*	1873886	026489018	Waiver	ORA/OBPO September 2021 VAI
(b) (4) *DP filling; DP release testing*	(b) (4)	(b) (4)	Waiver	ORA (b) (4) VAI
(b) (4) *DP release testing*	(b) (4)	(b) (4)	Waiver	ORA (b) (4) NAI

ORA: Office of Regulatory Affairs; OBPO: Office of Biological Products Operations; VAI: Voluntary Action Indicated; NAI: No Action Indicated

Emergent BioDefense Operations Lansing LLC

ORA/OBPO performed a surveillance inspection of Emergent BioDefense Operations Lansing LLC from September 21–29, 2021. A Form FDA 483 list of observations was issued at the end of the inspection. The firm responded to the observations, and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as VAI.

(b) (4)

ORA performed a surveillance inspection of (b) (4) A Form FDA 483 list of observations was issued at the end of the inspection. The firm responded to Form FDA 483, and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as VAI.

(b) (4)

(b) (4) is a DP release and stability testing facility. The most recent inspection of (b) (4) was a pre-approval inspection performed by ORA for the Center for Drug Evaluation and Research for a drug under their review from (b) (4). A Form FDA 483 list of observations was not issued, and the inspection was classified NAI.

e. Container/Closure System

The DP is filled into (b) (4) clear borosilicate glass vials with a 20 mm (b) (4) rubber stopper, coated with (b) (4) on the outer top for lubricity, and a 20 mm, flip-top aluminum overseal with a plastic button. The vials, stoppers, and seals are manufactured by (b) (4) performed the container closure integrity testing at the (b) (4), facility, employing the (b) (4) method. All acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment

4. Nonclinical Pharmacology/Toxicology

The applicant conducted a single-dose acute toxicity study, a repeat-dose safety toxicity study, a pre- and post-natal developmental and reproductive toxicity (DART) study, as well as a juvenile repeat-dose toxicology study. All these GLP-compliant toxicology studies were performed in rats, and animals were dosed with CYFENDUS via IM injection, the intended route for human use.

Nonclinical Safety Toxicology Studies

In the single-dose toxicity study, no treatment-related effects on clinical observations, body weights, or ocular condition, and no treatment-related macroscopic changes were noted at necropsy. The only effects were injection site reactions along with local inflammation, increase in spleen weight, and hyperplasia in lymphoid tissues of the spleen and draining lymph nodes.

Similar findings were observed in the repeat dose safety toxicity study in which animals were administered three IM injections (full human dose, 0.5 mL), two weeks apart. The changes in clinical pathology parameters, organ weights, and lymphoid tissues were consistent with immune stimulation. The injection site reactions were mild to marked necrosis accompanied by mild to moderate chronic, chronic-active, subacute or granulomatous inflammation, which often extended to the surrounding fascia and occasionally extended into the subcutis. Following the recovery period, no evidence of progression of those changes were noted after the treatment phase, and there was no evidence of any delayed toxicity associated with either the CpG 7909 adjuvant or CYFENDUS.

After the treatment phase, the injection site subacute inflammation was replaced by chronic inflammation characterized by chronic or granulomatous inflammatory infiltrates. The necrosis and granulomatous inflammation at the injection sites were considered adverse reactions and were expected to resolve over time. Additionally, the severity of the inflammatory effects at the injection site is likely exacerbation due to repeat administration of the test articles in the same (rather than alternating) site and the fact that in the rat, the muscle mass at the injection site is much less than in a human. The observed local and systemic inflammatory responses and findings are primarily due to the immunostimulatory effect of CpG 7909.

Developmental and Reproductive Toxicity Studies

In the DART study, female rats were injected with water for injection, adjuvant (CpG 7909 plus (b) (4) , or CYFENDUS (human dose). The animals received three doses of the test article: 14 Days prior to start of cohabitation, on the Day of cohabitation and on gestation Day 7. There was no mortality in females. No reproductive or developmental toxicity was noted in the DART study. There was no effect on mating, fertility, pregnancy, embryo-fetal viability, growth, or morphologic development, parturition, maternal care of offspring or postnatal survival, growth, or development. There was also no adverse maternal toxicity, with findings limited to non-adverse, transient injection site edema and injection site nodules. To support the potential pediatric use of CYFENDUS in the event of an anthrax emergency, a repeat-dose study was conducted in juvenile rats (3 Weeks old) where animals received three doses of vehicle only, adjuvant (CpG 7909 plus (b) (4) , or CYFENDUS (0.1 mL) one Week apart, starting at weaning. The findings in the juvenile toxicity study were transient and indicative of local and generalized immune system stimulation. At the injection site, mild to moderate inflammation with microscopic necroses (mild to marked) was observed as well as lymphoid hyperplasia of the draining lymph nodes and spleen. Partial recovery was observed for most of the observations. However, after the recovery phase, granulomatous inflammation was observed at the injection site. These inflammatory changes are considered treatment-related and adverse, but are expected to resolve over time.

Adequate data are presented to demonstrate safety and tolerability of the vaccine when administered IM. Overall, no findings of concern regarding vaccine safety were identified, and all these studies demonstrated a robust antibody response induced by CYFENDUS vaccination, supporting an immunogenic effect.

5. Clinical Pharmacology

Mechanism of Action

CYFENDUS is made up of *B. anthracis* cell-free filtrate that mainly contains 83-kDa PA, small amounts of (b) (4) , and additional poorly characterized proteins released during bacterial cell growth. Though all the components found in the cell-free filtrate may contribute to the efficacy of CYFENDUS to some extent, the principal protective immunogen is PA. An immune correlate of protection is unknown for PA. Antibodies raised against PA may contribute to protection by neutralizing the activities of anthrax toxins. The contribution to protection has not been determined for any additional protein or filtrate components present in the product.

CpG 7909 is a toll-like receptor 9 (TLR 9) agonist designed to induce an enhanced antigen-specific antibody response and a natural killer T-cell immune response. It stimulates TLR 9 expressing cells to induce an innate immune response characterized by the production of T-helper type 1 cells and proinflammatory cytokines[7].

6. Clinical/Statistical

Animal Efficacy Studies

Due to the rare occurrence of *B. anthracis* infections and the inability to conduct ethical studies exposing humans to anthrax, it is not feasible to conduct clinical-endpoint human efficacy studies. Therefore, Emergent is pursuing licensure of CYFENUDUS for a PEP indication under the Animal Rule (21 CFR Part 601, Subpart H, “Approval of Biological Products when Human Efficacy Studies are not Ethical or Feasible”).

The pathogenic mechanisms resulting in inhalational anthrax are well characterized and have been shown to closely resemble the human disease in both the rabbit and NHP aerosol challenge models. These served as the pivotal animal models supporting BioThrax PEP licensure. The activity of the CpG 7909 adjuvant has been observed to be significantly weaker in rabbits; therefore, to provide a suitable additional animal to demonstrate the effectiveness of CYFENDUS, the applicant developed and used a guinea pig model of inhalational anthrax. A natural history study of inhalational anthrax in guinea pigs demonstrated that the course of inhalational anthrax and the resulting pathology in guinea pigs were comparable to that seen in rabbits and the NHP.

To assess the effectiveness of the vaccine’s human dose, immune responses associated with survival in animals were bridged to human immunogenicity data to infer clinical benefit. The TNA assay was used to determine the threshold of protection for CYFENDUS.

In two guinea pig studies and two NHP studies, groups of animals were immunized on Days 0 and 28 with dilutions of CYFENDUS, a single dose level of BioThrax, or placebo (adjuvant alone or sterile saline). The animals were challenged on Day 70 with aerosolized *B. anthracis* spores. A 70% probability of survival was associated with Day 69 TNA NF_{50} titers ranging from 0.063 to 0.081 in the guinea pig studies and Day 70 TNA NF_{50} titers ranging from 0.107 to 0.262 in the NHP studies. These pre-exposure

studies with CYFENDUS in guinea pigs and the NHP demonstrated that the vaccine-induced immune response protected animals against death from anthrax in a dose-dependent manner.

To closely mimic the intended clinical regimen of AV7909 of two doses two weeks apart, the applicant conducted two additional animal studies: one in guinea pigs and one in NHP. Animals were immunized on Days 0 and 14 and challenged on Day 28, to determine whether protective TNA levels could be achieved at an earlier timepoint. These additional animal studies confirmed protection. Pre-challenge TNA NF_{50} titers of 0.072 for guinea pigs and 0.151 for NHPs were associated with a 70% probability of survival following challenge on Day 28. Pre-challenge TNA NF_{50} titers of 0.081 and 0.262 in guinea pigs and NHPs, respectively, were associated with a 70% probability of survival following challenge on Day 70.

In previous BioThrax studies, groups of rabbits or NHP were immunized on Days 0 and 28 with dilutions of BioThrax or placebo and challenged on Day 70 with aerosolized *B. anthracis* spores. A pre-exposure TNA NF_{50} level of 0.56 corresponded to a 70% probability of survival in rabbits, and a pre-exposure TNA NF_{50} level of 0.29 corresponded to a 70% probability of survival in the NHP.

Subsequently, five additional rabbit pre-exposure prophylaxis studies showed that TNA NF_{50} thresholds in the range of 0.19 to 0.29 correlated with 70% rabbit survival. Logistic regression analysis of pooled study data from these BioThrax immunized rabbits showed a TNA NF_{50} threshold of 0.24 associated with a 70% probability of survival. The NF_{50} value of 0.24 obtained from the pooled rabbit data analysis is consistent with the NF_{50} value of 0.29 obtained in the BioThrax NHP study for licensure of the BioThrax PEP indication. The results of the five additional rabbit studies suggest that the original rabbit study yielding the 0.56 NF_{50} threshold overestimated the TNA threshold level, likely due to the deaths of several rabbits that had high TNA titers (NF_{50} > 0.6). Based on these results, the applicant proposed using the BioThrax-immunized NHP TNA threshold of protection NF_{50} level from the NHP study (0.294 NF_{50}) as an acceptable bridging endpoint for the proposed AV7909 Phase 3 trial co-primary endpoint, to which CBER agreed. Additionally, a TNA NF_{50} threshold of 0.29 was used as the target protective threshold for the non-inferiority comparison between BioThrax and CYFENDUS.

The applicant also conducted a proof-of-concept study in guinea pigs to evaluate the ability of post-exposure vaccination with CYFENDUS to increase animal survival compared to that observed with post-exposure antibiotic treatment alone. Mortality data demonstrated that CYFENDUS, when administered in conjunction with ciprofloxacin, protected guinea pigs from death due to anthrax in a dose-dependent manner and provided a significant added survival benefit compared to the ciprofloxacin treatment alone. This study demonstrated the added benefit of concomitant administration of CYFENDUS with antibiotic relative to antibiotic treatment alone.

The animal studies demonstrated that CYFENDUS induced a rapid TNA response that protected a large proportion of animals from death due to inhalational anthrax in a dose-dependent manner. These studies provide supportive animal data for CYFENDUS PEP licensure and support the TNF NF_{50} thresholds selected to estimate protection in the human clinical studies.

No deficiencies were identified with the nonclinical animal studies

a. Clinical Program

General Overview of human clinical studies

The applicant included data from four clinical studies in the BLA to support the safety and immunogenicity of CYFENDUS. The clinical investigational name of CYFENDUS is AV7909. The clinical studies discussed in this SBRA are listed in Table 7.

Table 7: Overview of the US clinical studies supporting the BLA

Study Number	Description	Dosing Regimen and Number of Participants Randomized
EBS.AVA.201 (NCT# 01263691)	Phase 1, parallel-arm, double-blind, randomized, placebo-controlled, dose-ranging study to evaluate the safety, tolerability, and immunogenicity of AV7909 in adults 18 to 50 years of age	2 IM injections at 0 and 2 Weeks Arm 1 (0.5 mL BioThrax): 18 Arm 2 (0.5 mL AVA + 0.5 mg CpG 7909): 18 Arm 3 (0.5 mL AVA + 0.25 mg CpG 7909): 17 Arm 4 (0.25 mL AVA + 0.5 mg CpG 7909): 19 Arm 5 (0.25 mL AVA + 0.25 mg CpG 7909): 18 Arm 6 (saline or Placebo): 15
EBS.AVA.208 (NCT# 01770743)	Phase 2, randomized, double-blind, active-controlled study to evaluate the safety and immunogenicity of three immunization schedules and two dose levels of AV7909 in adults 18 to 50 years of age	3 IM injections at 0, 2, and 4 Weeks Arm 1 (AV7909, IM, Days 1 and 15): 44 Arm 2 (AV7909, IM, Days 1 and 29): 34 Arm 3 (AV7909, IM, Days 1, 15, and 29): 23 Arm 4 (Half dose AV7909, IM, Days 1, 15, and 29): 44 Arm 5 (BioThrax, IM, Days 1, 15, and 29):23
EBS.AVA.210 (NCT# 04067011)	Phase 2, open-label study in adults 18 to 45 years of age to evaluate potential interactions of AV7909 vaccination with ciprofloxacin or doxycycline when administered concomitantly	2 IM injections at 0 and 2 Weeks Arm 1(AV7909 + ciprofloxacin): 70 Arm 2 (AV7909 + doxycycline): 71 Arm 3 (AV7909 only): 64
EBS.AVA.212 (NCT# 03877926)	Phase 3, randomized, double-blind study in adults 18 to 65 years of age to evaluate the safety, lot consistency, and immunogenicity of AV7909	3 injections at 0, 2, and 4 Weeks AV7909 (Lot 1, IM, Days 1 and 15): 1053 AV7909 (Lot 2, IM, Days 1 and 15): 1054

Study Number	Description	Dosing Regimen and Number of Participants Randomized
		AV7909 (Lot 3, IM, Days 1 and 15): 1049 BioThrax (SC, Days 1, 15, and 29): 553

Due to data integrity issues identified at study site US1027 in Study EBS.AVA.212, all results presented in this document exclude data from this site, with the exception of maternal fetal outcomes in the safety analysis, which include pregnancy data from study site US1027. The proportion of subjects is presented in form of percent (%) of subjects.

Study EBS.AVA.201 (Dose Selection)

Study EBS.AVA.201 was a Phase 1, randomized, double-blind, parallel-arm, placebo-controlled, dose selection, multicenter study evaluating the safety, tolerability, and immunogenicity of the vaccine in healthy adults 18 to 50 years of age. A total of 105 subjects were randomized to one of six Arms in which subjects received BioThrax (Arm 1), one of four different formulations of AV7909 (Arms 2 to 5), or saline (Arm 6). The primary objective of the study was safety evaluation. The secondary objective was to evaluate immunogenicity, as determined by peak geometric mean titer (GMT) TNA NF_{50}, and time to achieve peak antibody titer. The safety monitoring comprised an evaluation of concomitant medication use, physical examination (PE), local and systemic reactogenicity, unsolicited adverse events (AEs), treatment emergent AEs (TEAEs), serious AEs (SAEs), adverse events of special interests (AESIs) of autoimmune etiology, and laboratory testing, from Day 0 through Day 84.

All four formulations of AV7909 were safe and immunogenic when administered IM as a two-dose series on Days 0 and 14. The most frequently reported TEAEs were injection site reactions of mild to moderate severity with no association between TEAE rate and the amount of AVA or CpG 7909 per dose. No SAEs related to AV7909 were reported. No AESIs were reported. There was one pregnancy in the placebo arm with subsequent birth of a healthy, full-term infant.

The percentage of subjects reaching the TNA NF_{50} value of 0.56 at Days 28, 35, and 42 were 94.1% to 100% for the 0.5 mL AVA plus 0.5 mg CpG 7909 Arm (formulation 1), 93.8% for the 0.5 mL AVA plus 0.25 mg CpG 7909 Arm (formulation 2), and 88.2% to 88.9% for the 0.25 mL AVA plus 0.5 mg CpG 7909 Arm (formulation 3). Peak TNA NF_{50} responses were achieved at Day 28 for all four formulations of AV7909 and at Day 35 for BioThrax group. There was a steady decline in TNA NF_{50} GMTs after Day 28. By Day 84, TNA NF_{50} GMTs for all the AV7909 groups were still higher than baseline levels, whereas TNA NF_{50} GMTs for BioThrax remained close to the baseline levels. Out of all the study groups, the formulation 2 (0.5 mL AVA+ 0.25 mg CpG 7909) Arm had the highest GMT peak value at Day 28 with 81% of subjects achieving TNA NF_{50} value of ≥0.56 at Day 70.

Based on the safety and immunogenicity data obtained from EBS.AVA.201, formulation 2 of AV7909 was selected for further clinical evaluation.

Study EBS.AVA.208 (Dose Schedule Finding)

Study EBS.AVA.208 was a Phase 2, randomized, double-blind, active-controlled, parallel-arm, multicenter study evaluating the safety and immunogenicity of AV7909 for PEP of anthrax disease in 168 healthy adults 18 to 50 years of age. The purpose of the study was to assess different dosing schedules of the AV7909 formulation selected as optimal from the Phase 1 study EBS.AVA.201 (AVA 0.5 mL plus 0.25 mg CpG 7909), when compared to half-dose AV7909 and BioThrax, to select the dosing regimen for further clinical development in the Phase 3 trial. Subjects were randomized using a 4:3:2:4:2 ratio to one of five Arms comprising three immunization schedules: two doses of full dose AV7909 2 weeks apart (Arm 1) or 4 weeks apart (Arm 2), or three doses of full dose AV7909 2 weeks apart (Arm 3), or three half dose levels of AV7909 2 weeks apart (Arm 4), or three doses of BioThrax 2 weeks apart (Arm 5) (See Table 7 above).

Study endpoints are provided below.

Primary immunogenicity endpoint:

- Lower bound (LB) of the 95% confidence intervals (CIs) of ≥ 40% for the percentage of subjects in each study group with Day 63 TNA NF_{50} values ≥ 0.56

Secondary immunogenicity endpoints:

- Percent of subjects in study Groups 1, 3, and 4; with Day 28 TNA NF_{50} values ≥ 0.56
- Percent of subjects in each study group with Day 42 TNA NF_{50} values ≥ 0.56
- Percent of subjects achieving a specified TNA NF_{50} value at each time point and exact Binomial 95% CIs of point estimates of percentages
- Geometric mean (GM) of the TNA NF_{50} values at each time point (Days 0, 21, 28, 35, 42, 49, 63, and 84) with 95% CIs around the point estimate. The 95% CIs for the GM values and ratios of GM values using TNA NF_{50} (AV7909 vs. BioThrax) obtained by using anti-log values of 95% CIs for log10 TNA NF_{50}

Safety was evaluated by daily assessment of reactogenicity (solicited systemic and injection site reactions) for 7 consecutive days after each vaccination by e-diary card and by in-clinic assessment of reactogenicity on Days 7, 14, 21, 28, 35, and 42, and at other visits as applicable. TEAEs were assessed through Day 84 of the study. SAEs and AESIs were reported through 12 months after the last vaccination. Most subjects (76.8%) experienced TEAEs, which were mild to moderate in severity across all study groups and generally related to reactogenicity. No deaths were reported in this study. There were 3 subjects with 4 SAEs, all deemed unrelated to the vaccine. No AESIs were reported through the 12-month safety follow-up. In the study, four pregnancies were reported after Day 84. An SAE of neonatal atelectasis was reported in one pregnancy due to premature birth at 36 weeks. The other 3 pregnancies resulted in birth of healthy infants.

Of all the dosing schedules evaluated in this study, the highest percent of subjects (100%) achieved GMTs TNA NF_{50} ≥0.56 at Day 63 in Arm 2 (two-dose of AV7909, 4 weeks apart schedule) and Arm 3 (three full doses of AV7909, 2 weeks apart schedule) followed by 90.2% subjects in Arm 4 (three half-dose AV7909 regimen), 56.8% subjects in Arm 1 (two-doses of AV7909, two weeks apart), and 52.4% subjects in Arm 5

(BioThrax three-dose IM regimen). Kinetics of the AV7909 immune response when assessed by GMTs indicate peak immune response at Day 42 and a similar decline in GMTs for the two-dose regimen of AV7909 given on Week 0 and 2 and the three-dose BioThrax regimen.

Although the AV7909 three-dose schedule induced a higher TNA NF_{50} response compared to the two-dose AV7909 regimen, the two-dose AV7909 regimen was considered as the optimal dosing regimen for anthrax PEP since a higher peak immune response earlier post-vaccination is considered important in the PEP setting especially since AV7909 administration would be adjunct treatment to required antimicrobial therapy; with an anamnestic immune response critical at later time points post-vaccination for protection against disease due to *B. anthracis* exposure. Use of a two-dose AV7909 regimen in the PEP setting was also favored by less frequent and severe local and systemic reactogenicity than observed with the other AV7909 dosing regimens and ease of administration.

Study EBS.AVA.210 (Pharmacokinetics, concomitant administration)

Study EBS.AVA.210 was a Phase 2, open-label, multi-center study evaluating the effect of AV7909 administration on the pharmacokinetics (PK) of ciprofloxacin or doxycycline, when administered orally prior to and following administration of two-dose regimen AV7909 that was given two weeks apart, in subjects 18 to 45 years of age. Both antibacterial drugs are stockpiled by the US government for PEP of anthrax disease and may be used concomitantly with AV7909 in a mass exposure event.

A total of four sites in the US participated in this study. The 210 eligible subjects were randomized 1:1:1 into three study groups (AV7909 plus ciprofloxacin, AV7909 plus doxycycline, or AV7909 alone), with and without PK assessment. The primary objective was to demonstrate that ciprofloxacin and doxycycline steady-state PK measured after AV7909 vaccination were equivalent (via a 1.25-fold equivalence margin) to those measured prior to AV7909 vaccination. The secondary objective was to demonstrate that the immune responses to AV7909 in conjunction with ciprofloxacin or doxycycline were noninferior (via a 2-fold margin) to the immune responses to AV7909 administered alone.

Study endpoints for the AV7909-antimicrobial interference study comprise the following:

Co-Primary PK Endpoints:

- Area under the curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) and maximum concentration (C_{max}) for ciprofloxacin on Days 8 (prior to AV7909 vaccination) and 35 (following two doses of AV7909).
- $AUC_{0\text{-}12h}$ and C_{max} for doxycycline on Days 8 (prior to AV7909 vaccination) and 38 (following two doses of AV7909).

Secondary PK Endpoints:

- Assessment of the safety of concomitant administration of oral ciprofloxacin or doxycycline and two doses of AV7909 administered IM.

- Evaluation of the Day 37 immune response using the TNA assay following two IM doses of AV7909 with and without the concurrent oral administration of ciprofloxacin or doxycycline.

Secondary Immunogenicity Endpoints:

- TNA NF_{50} values on Day 37 for AV7909 alone, AV7909 + ciprofloxacin and AV7909 + doxycycline must be ≥ 0.5.

A summary of the study's analysis populations is provided in Table 8 below.

Table 8: EBS.AVA.210: Analysis Populations

	Cipro + AV7909	**Cipro + AV7909**	**Cipro + AV7909**	**Doxy + AV7909**	**Doxy + AV7909**	**Doxy + AV7909**	**AV7909 Alone**	**TOTAL**
Analysis Population	Group 1A n (%)	Group 1B n (%)	Group 1 (1A + 1B) n (%)	Group 2A n (%)	Group 2B n (%)	Group 2 (2A + 2B) n (%)	Group 3 n (%)	n (%)
Intent-to-Treat (ITT)[1]	45 (100.0)	25 (100.0)	70 (100.0)	45 (100.0)	26 (100.0)	71 (100.0)	69 (100.0)	210 (100.0)
Safety[2]	41 (91.1)	21 (84.0)	62 (88.6)	42 (93.3)	22 (84.6)	64 (90.1)	64 (92.8)	190 (90.5)
PK[3]	25 (55.6)	NA	NA	31 (68.9)	NA	NA	NA	NA
Immunogenicity[4]	28 (62.2)	19 (76.0)	47 (67.1)	36 (80.0)	14 (53.8)	50 (70.4)	54 (78.3)	151 (71.9)

n = number of subjects; % = percent of subjects. NA: Not applicable

Treatment groups:

Group 1A = AV7909 + ciprofloxacin (with PK assessment)
Group 1B = AV7909 + ciprofloxacin (without PK assessment)
Group 2A = AV7909 + doxycycline (with PK assessment)
Group 2B = AV7909 + doxycycline (without PK assessment)
Group 3 = AV7909 only

[1]The ITT Population included all randomized subjects
[2]The Safety Population included all randomized subjects who received at least one dose of either antibiotic or AV7909
[3]The PK and [4]Immunogenicity Population included subjects who were randomized and met the criteria as specified in the protocol

For the primary PK endpoint, equivalence (no interaction) of steady-state parameters prior to (Day 8) and after AV7909 coadministration (Day 35) were met in terms of the $AUC_{0\text{-}12h}$ (Geometric Mean Ratio [GMR] = 0.98; 90% Confidence Interval [CI]: 0.89 to 1.07) and C_{max} (GMR = 0.97; 90% CI: 0.87 to 1.08) for ciprofloxacin. For doxycycline, equivalence of steady-state PK parameters was met for $AUC_{0\text{-}12h}$ (GMR = 0.92; 90% CI: 0.82 to 1.03), but not for C_{max} (GMR = 0.90; 90% CI: 0.78 to 1.03). These findings of steady-state and single-dose PK differences for doxycycline pre- versus post-AV7909 vaccine are not clinically relevant in a PEP setting where doxycycline would be administered with AV7909.

The TNA NF_{50} GMT in the AV7909 plus ciprofloxacin group was noninferior to that of the AV7909 alone group (GMR=1.13 with 95% CI 0.78 to 1.64). In the AV7909 plus doxycycline group, the GMR was 1.14 with 95% CI 0.81 to 1.60. Day 37 TNA NF_{50} GMTs in coadministration Arms 1 and 2 were generally similar to the single administration Arm 3 in subgroup analyses by age and sex.

Safety in all the tested Arms was assessed by collecting AEs up to Day 51. SAEs and AESIs were collected for 12 months after the second dose of AV7909. The most frequently reported reactions in all groups were tenderness (75.9% to 84.7%), pain (70.7 to 84.4%), and muscle ache (60.3% to 70.3%). The percentages of participants reporting any injection site reaction were similar between Arms, whereas the percentage reporting any systemic reaction was slightly lower in the AV7909 plus ciprofloxacin group. There was one pregnancy reported in this study that led to birth of a full-term healthy infant. No deaths or AESIs were reported in this study.

No clinically significant interaction between the 2-dose regimen of AV7909 and ciprofloxacin or doxycycline was observed. The observations remained within the pre-specified statistical parameters defined for this study and were supported by results for both ciprofloxacin and doxycycline in the rhesus monkey anthrax model. There were no significant safety concerns observed for AV7909 either as a single administration or in conjunction with ciprofloxacin or doxycycline.

Study EBS.AVA.212 (lot to lot consistency, immunogenicity, non-inferiority)

EBS.AVA.212 was the Phase 3, double-blind, randomized, multicenter, active-controlled (BioThrax), parallel-arm, safety, lot-to-lot consistency, and immunogenicity study conducted in 3689 healthy adults 18 to 65 years of age. In this study AV7909 (Lots 1-3, Groups 1-3) was administered IM on Days 1 and 15, with matching placebo given on Day 29. BioThrax administered under the PEP schedule as three SC injections on Days 1, 15, and 29 (Group 4), served as a comparator vaccine. A total of 35 sites in the US participated in the study. The following are the objectives and the endpoints of this Phase 3 study. The proportion of subjects is presented in form of percent of subjects.

Primary objectives:

- Demonstrate lot consistency following a two-dose schedule of AV7909 administered IM in healthy adults.
- Demonstrate immunogenicity on Day 64 following two-dose schedule of AV7909 administered IM in healthy adults.
- Demonstrate non-inferiority of a two-dose schedule of AV7909 administered IM to the licensed three-dose schedule of BioThrax administered SC in healthy adults.
- Evaluate safety following AV7909 two-dose dose schedule administered IM.

The secondary objective was to demonstrate immunogenicity on Day 29 following a two-dose schedule of AV7909 administered IM in healthy adults.

The following were the primary immunogenicity and safety endpoints.

Co-primary immunogenicity endpoints with success criteria:

1. Demonstration of lot-to-lot consistency of AV7909
    - GMT Ratio of TNA NF_{50} at Day 64

    Success Criteria: This endpoint was met if the 95% CIs for the Day 64 TNA NF_{50} GMT ratios between all three pairs of AV7909 groups (Lot 1 versus (vs.) Lot 2, Lot 2 vs. Lot 3, and Lot 1 vs. Lot 3) were within 0.5 and 2.0.

- Lot Consistency and Immunogenicity of AV7909 evaluated with percent of subjects with TNA NF50 ≥0.56 at Day 64

Success Criteria: The protective level of immunogenicity in all three lots was demonstrated if the lower bound (LB) of the 2-sided 95% CI is ≥40% for the percentage of subjects in each of the three AV7909 lots achieving a TNA NF_{50} ≥0.56.

2. Demonstration of immunogenicity of AV7909 at Day 64 using a non-inferiority comparison to BioThrax
    - Immunogenicity of the 3 pooled AV7909 lots compared to BioThrax, as defined by the percent of subjects with a TNA NF_{50} value of ≥0.56.

    Success Criteria: The LB for the 2-sided 95% CI for the percentage of subjects with TNA NF_{50} values above the specified threshold of protection (≥0.56) was ≥40%.

    - Comparison of the percentage of Subjects with a TNA NF_{50} ≥0.29, AV7909 vs. BioThrax.

    Success Criteria: Non-inferiority demonstrated if the LB of the 2-sided 95% CI for the difference in the percentage of subjects (AV7909 lots combined – BioThrax) is above -15%.

Safety Endpoints:

- Evaluation of the safety of AV7909 in healthy adults following a two dose AV7909 schedule administered IM.

For the lot-to-lot consistency, each group received a specific lot of AV7909. Vaccinations were administered in the clinic by blinded, authorized personnel. Subjects were observed for 30 minutes after each vaccination for adverse effects, including anaphylaxis.

Blood samples for immunogenicity testing were collected on Days 1, 29, and 64. Solicited local and systemic reactions were assessed for at least seven days after each vaccination. AEs, SAEs, and AESIs were collected up to Day 394.

All immunogenicity and lot consistency analyses were based on the Per-Protocol Population (subjects who were randomized and did not have any of the protocol deviations). No imputation was made for the missing data. All safety analyses were performed based on EBS.AVA.212 immunogenicity and safety populations as summarized in Table 9, below.

Table 9: Analysis Population (excluding study site US1027)

Analysis Population	**AV7909 Lot 1** **n (%)**	**AV7909 Lot 2** **n (%)**	**AV7909 Lot 3** **n (%)**	**AV7909 (Pooled)** **n (%)**	**BioThrax** **n (%)**	**TOTAL** **n (%)**
Intent-to-Treat (ITT)	1053 (100.0)	1054 (100.0)	1049 (100.0)	3156 (100.0)	533 (100.0)	3689 (100.0)
Safety	1050 (99.7)	1053 (>99.9)	1048 (>99.9)	3151 (99.8)	533 (100.0)	3684 (99.9)

Analysis Population	AV7909 Lot 1 n (%)	AV7909 Lot 2 n (%)	AV7909 Lot 3 n (%)	AV7909 (Pooled) n (%)	BioThrax n (%)	TOTAL n (%)
Per Protocol (Immunogenicity)	835 (79.3)	854 (81.0)	854 (81.4)	2543 (80.6)	430 (80.7)	2973 (80.6)

n: number of subjects
%: percent of subjects based on number of randomized subjects

The pre-specified criteria for the two immunogenicity co-primary endpoints at Day 64 were met, thereby demonstrating both lot consistency across the three AV7909 lots and protective immunity. The 95% CI for ratio of GMT TNA NF_{50} at Day 64 was within the pre-defined criteria of 0.5 and 2.0 and was indicative of equivalent immunogenicity across the three consecutive AV7909 lots. A protective level of immunogenicity at Day 64 (TNA NF_{50} ≥0.56) after IM administration of the second dose of the two-dose schedule of AV7909 in the pooled group of AV7909 was achieved in 66.3% subjects. The results for the first co-primary endpoint are summarized in Table 10.

Table 10: EBS.AVA.212 First co-primary immunogenicity endpoint summary

Percent of Subjects with a TNA NF_{50} value of ≥0.56 at Day 64	AV7909 Lot 1 (N=878)	AV7909 Lot 2 (N=896)	AV7909 Lot 3 (N=896)	AV7909 (Three Lots Pooled) (N=2670)	BioThrax (N=454)
n	835	854	854	2543	430
GMT	0.765	0.741	0.716	0.740	0.330
Lower 95% CI	0.718	0.698	0.673	0.714	0.299
Upper 95% CI	0.814	0.788	0.762	0.767	0.363
Percent of subjects with TNA NF_{50} ≥0.56	68.9%	65.6%	64.4%	66.3%	31.2%
95% CI	65.6, 72.0	62.3, 68.8	61.1, 67.6	64.4, 68.1	26.8, 35.8

N = Number of subjects per study group in the Per-Protocol population
n = Number of subjects achieving a TNA NF_{50} cut-off value based on Per-Protocol population
% = Percent of subjects achieving a TNA NF_{50} cut-off value based on Per-Protocol population
GMT = Geometric mean titer
CI = Confidence interval

The lower bound of the two-sided 95% CI for the difference (AV7909 – BioThrax) in the percentage of subjects with TNA NF_{50} values of ≥0.29 on Day 64 in the combined AV7909 Group vs. BioThrax Group was greater (25.2%) than the pre-defined criterion of -15%. Thus, the immune response at Day 64 in subjects who received AV7909 was determined as non-inferior to the immune response at Day 64 in subjects who received BioThrax. Table 11 shows results for second co-primary immunogenicity endpoint for non-inferiority of CYFENDUS to BioThrax.

Table 11: EBS.AVA.212, second co primary immunogenicity endpoint for non-inferiority of AV7909 to BioThrax

Percent of Subjects with a TNA NF_{50} ≥0.29 at Day 64	AV7909 Pooled (N=2543)	BioThrax (N=430)
Percent of subjects with TNA NF_{50} ≥0.29	86.6%	61.4%

Percent of Subjects with a TNA NF_{50} ≥0.29 at Day 64	AV7909 Pooled (N=2543)	BioThrax (N=430)
95% CI	85.2, 87.9	56.6, 66.0

N = Number of subjects per study group in the Per-Protocol population
% = Percent of subjects achieving a TNA NF_{50} cut-off value based on Per-Protocol population

In study EBS.AVA.212 the success criteria for both co-primary immunogenicity endpoints were met for AV7909, demonstrating a protective level of immunity per the Animal Rule at Day 64. All secondary immunogenicity endpoints were also met in this Phase 3 study.

Subgroup analyses by age, sex, and race were performed with no formal statistical hypothesis testing. The analyses of immunogenicity indicated that immune responses trended higher in younger subjects (18 to 30 years). There was no significant difference in the immune response in AV7909-vaccinated subjects when evaluated by sex or racial subgroup.

Safety was assessed in 3151 AV7909 recipients in this study. The most commonly reported injection site reactions among AV7909 recipients after any vaccination were tenderness (88.1%), pain (86.3%), and arm motion limitation (63.7%). The most common systemic reactions in AV7909 vaccinated subjects comprised muscle ache (75.2%), tiredness (67.1%), and headache (58.0%). The severity of both local and systemic reactions in AV7909-vaccinated subjects was generally Grade 1 or 2. Grade 3 reactions were very infrequent, and no Grade 4 local or systemic reactions were reported. Frequencies of local reactions were slightly higher among BioThrax recipients than among AV7909 recipients, while frequencies of systemic reactions were slightly higher among AV7909 recipients. There were 15 incidences of confirmed AESIs in the combined AV7909 Group (15/3151 subjects, 0.5%). The majority of AESIs were deemed unrelated to vaccine administration. There were 32 total pregnancies reported in 28 subjects (two twin pregnancies) in the AV7909 Group, with birth of 15 full-term healthy infants, birth of two full-term infants with congenital abnormalities (biliary cyst and labial tie, respectively), and seven miscarriages. A total of six deaths were reported in this study, all of whom received AV7909 and were considered unrelated to study vaccination by the investigator. There were no notable differences in the percentages of participants reporting any AE leading to vaccination discontinuation, AE leading to study withdrawal, or AESI between arms.

In general, AV7909 appeared to be well tolerated with no significant safety concerns identified in EBS.AVA.212.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

BIMO inspections were performed at one nonclinical laboratory that conducted two animal efficacy studies (Protocols 3580-100069467 and 3655-10072763, under the Animal Rule), and at six clinical study sites that participated in the conduct of two studies conducted in humans (EBS.AVA.210 and EBS.AVA.212). The six clinical study site inspections included a For-Cause inspection that was conducted at study site US1027 due to Good Clinical Practice noncompliance issues that were reported by the applicant in the BLA. Due to these noncompliance issues, the data obtained from study site US1027 were removed from the safety analyses. No significant deviations were noted for

the inspection of the nonclinical studies, and a Form FDA 483 was not issued at the close of the inspection. Out of the six clinical study sites inspected, three sites were issued FDA Form 483 at the close of the inspection. The inspectional issues noted on the FDA Forms 483 for those three sites were resolved. No significant deviations were observed at the other three inspected clinical study sites. Overall, the inspections of the clinical study sites except study site US1027 did not reveal substantive issues that impact the information and data submitted in the BLA.

c. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups must be submitted at the time an application for a new active ingredient, new dosage form, new dosing regimen, new indication, or new route of administration is submitted, unless this requirement for assessment is waive, deferred, or inapplicable.

Emergent developed CYFENDUS for the PEP indication under the FDA Animal Rule (21 CFR Part 601, Subpart H, “Approval of Biological Products when Human Efficacy Studies are not Ethical or Feasible”).

On August 19, 2021 CYFENDUS was granted Orphan Drug Designation (DRU-2021-8325) for “post-exposure prophylaxis of anthrax disease resulting from suspected or confirmed exposure to *Bacillus anthracis*”. In accordance with §21 Code of Federal Regulations (CFR) 601.27 (d) any product for an indication for which Orphan Drug Designation is granted is exempt from pediatric studies under the Pediatric Research Equity Act (PREA).

Under the Orphan Drug Law, this application qualified for a complete waiver of PREA requirements.

7. Safety and Pharmacovigilance

Safety Results

Safety of CYFENDUS was assessed in 3276 participants who received at least one dose of the to-be-marketed formulation and dosing regimen of the vaccine in four clinical studies. Of this total, 3017 participants received both doses of CYFENDUS. Of the 533 BioThrax recipients, 21 (3.9%) received two doses and 472 (88.6%) received all three doses of the comparator vaccine. A majority of the participants were white (77.9% AV7909 group and 78.0% BioThrax group). The median age for the safety population was 38 years, with a slightly higher proportion of females (57.8%).

Safety evaluation methods were generally consistent across all four studies, however symptoms solicited for assessment of local and systemic reactogenicity were inconsistent across the four clinical studies; therefore, pooling of reactogenicity data across the four clinical studies was not considered appropriate. Study EBS.AVA.212 contributed the majority of subjects to the overall safety database, therefore reactogenicity reported in Study EBS.AVA. 212 was selected for including in the prescribing information.

AEs and AESIs were followed from the day of first vaccination through 12 months post last vaccination dose. The integrated safety results, which summarized safety findings for all four clinical studies, did not identify any new safety concerns due to CYFENDUS administration.

TEAEs in the four studies are included in the pooled analyses The most frequently reported TEAEs in CYFENDUS recipients (N=3276) were injection site reactions and comprised the following (≥2% frequency): injection site pain (4.6%), vaccine complication (3.8%), upper respiratory infection (3.2%), musculoskeletal complication (2.9%), procedural headache (2.7%), and injections site induration (2.3%). The majority of TEAEs were related to injection site reactions or systemic reactogenicity after vaccination. Upper respiratory tract infection was deemed unrelated to AV7909. The majority of TEAEs reported were Grade 1 or 2 in severity.

A higher percentage of BioThrax recipients reported any AE, while a higher percentage of CYFENDUS recipients (1.8%) reported any SAE compared with BioThrax recipients (0.8%). Most of the SAEs reported were not related to CYFENDUS.

A total of six deaths were reported, all of whom were administered the (b) (4) dosing regimen/formulation of the vaccine (Study EBS.AVA.212), with none assessed by the study investigator as related to AV7909.

A total of 15 AESIs (3 endocrine, 2 gastrointestinal, 3 musculoskeletal and connective tissue, and 7 of dermatologic category) occurred after CYFENDUS vaccination. Three events in three subjects (ulcerative colitis, diffuse alopecia, and chronic spontaneous urticaria) were adjudicated as possibly related to the vaccination.

A total of 35 pregnancies were reported in 33 female subjects (two twin gestations) who received AV7909. Eleven subjects were exposed to the vaccine either in the first trimester (n=10) or 30 days prior to pregnancy onset (n=1). Of the 11 pregnancies (one twin pregnancy), 1 (9.1%) resulted in miscarriage and there were 2 infants (18.2 %) born with major birth defects. Most pregnancies resulted in full-term births of healthy infants. Apart from congenital malformations seen in a twin birth in Study EBS.AVA.212 that was considered possibly related to vaccination by the investigator, all pregnancy outcomes reported were deemed unrelated to treatment.

The available safety data do not substantiate a need for safety-related postmarketing studies.

Pharmacovigilance Plan

Emergent submitted a routine Risk Management Plan (RMP) that includes a Pharmacovigilance Plan (PVP) for CYFENDUS to address “Important Potential Risks” and “Missing Information” as experienced in the clinical trials. The proposed pharmacovigilance (adverse reactions reporting and signal detection) plan for CYFENDUS included in the RMP is adequate for the labeled indication. A separate pregnancy registry for CYFENDUS will not be conducted, as the intended use is for a PEP scenario and not for active immunization. The available safety data do not

substantiate a need for a Risk Evaluation and Mitigation Strategy, a postmarketing commitment, or a postmarketing requirement (PMR) study, except the required field study as mentioned below.

8. Labeling

The proposed proprietary name, CYFENDUS, was reviewed by CBER's Advertising and Promotional Labeling Branch (APLB) on June 30, 2022 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on July 18, 2022.

APLB reviewed the proposed Package Insert (PI), Patient Package Insert, package, and container labels on May 16, 2023, and found them acceptable from a promotional and comprehension perspective.

The Review Committee negotiated revisions to the PI for: exclusion of the safety data from study site US1027; exclusion of any subjects from the safety analyses with reported missing information; inclusion of updated pregnancy data from CYFENDUS and BioThrax pregnancy registry; and including BioThrax AE information under postmarketing experience section.

All labeling issues regarding the PI and the carton and container labels were acceptably resolved after exchange of information and discussions with the applicant.

9. Advisory Committee Meeting

This submission was not discussed at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting because FDA review of this submission did not identify concerns or issues that would have benefited from an advisory committee discussion and the submission was consistent with the recommendations from the 2010 VRBPAC meeting[3].

10. Other Relevant Regulatory Issues

The pre-license inspection for the DS and DP manufacturing facilities and the final release testing facility are waived based on their inspection histories and compliance status. The basis for waiving the inspection of these facilities is documented in a separate inspection waiver memo dated March 27, 2023.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on a review of the clinical, non-clinical, and product-related data submitted in the original BLA, the Review Committee recommends approval of CYFENDUS for the labeled indication and usage.

b. Benefit/Risk Assessment

The applicant has submitted data to support the safety and reasonable likelihood of benefit when CYFENDUS is administered in combination with a recommended course of appropriate antimicrobial therapy, for PEP of disease resulting from suspected or confirmed *B. anthracis* exposure in persons 18 through 65 years of age. The Review Committee agrees that the risk/benefit balance for CYFENDUS is favorable and supports approval for use in adults 18 through 65 years of age

c. Recommendation for Postmarketing Activities

The applicant has submitted a routine PVP that is acceptable, and there is no need for a pregnancy registry. As required under 21 CFR 601.91(b)(1), the applicant submitted a draft protocol synopsis (EBS.AVA.213) to assess the clinical benefit and safety of CYFENDUS in the post-exposure setting, should an inhalational anthrax event occur in the US. The applicant has agreed to the following Postmarketing Requirement (PMR), which is specified in the approval letter.

1. To conduct a field study to evaluate the clinical benefit and safety of CYFENDUS when administered in conjunction with recommended antibacterial drugs for post-exposure prophylaxis following a *Bacillus anthracis* mass exposure event. The study will be conducted as a PMR under regulations for products approved under the Animal Rule, 21 CFR 601.91(b)(1).

Final Protocol Submission: March 31, 2024

Study Completion: To be determined should an event occur

Final Report Submission: To be determined should an event occur

12. References

1. Package Insert and Information for Patients-BioThrax, November 2015 (https://www.fda.gov/media/71954/download)
2. Bower W.A., Schiffer J., Robert L., et al. Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2019. MMWR Recomm and Reports 2019, 68(19):1-14 (https://www.cdc.gov/mmwr/volumes/68/rr/rr6804a1.htm)
3. Transcript of FDA Advisory Committee VRBPAC Meeting, 16 November 2010. https://wayback.archiveit.org/7993/20161023022525/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm237045.htm
4. Summary Basis for Regulatory Action. BioThrax. https://wayback.archive-it.org/7993/20170722071225/https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM308410.pdf
5. Bower W.A., Hendricks K., Pillai S., et al. Clinical framework and medical countermeasures use during an anthrax mass-casualty incident, CDC

Recommendations. MMWR Recomm Rep 2015; 64(4):1-19. (https://www.cdc.gov/mmwr/pdf/rr/rr6404.pdf)

6. Li H., Soroka D.S., Taylor T.H., et al. Standardized, mathematical model-based and validated in vitro analysis of anthrax lethal toxin neutralization. J Immunol Methods. 2008; 333(1-2):89-106
7. Bode C., Zhao G., Steinhagen F., et al. CpG DNA as a vaccine adjuvant. Expert Rev Vaccines. 2011; 10(4):499-511.