



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

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To: Chair, Review Committee
Office of Vaccine Research and Review (OVR)

Through: Adamma Mba-Jonas, MD, MPH
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Director, DPV

Subject: Review of Pharmacovigilance Plan

Sponsor: Emergent BioSolutions

Product: anthrax vaccine adsorbed, adjuvanted; CYFENDUS

Application Number: BLA 125761.0

Proposed Indication: 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 regimen

Submission Date: 4/20/2022

Major Amendment: 9/9/2022

Action Due Date: 7/20/2023

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the Sponsor's Pharmacovigilance Plan (PVP) submitted under the original BLA (125761.0) based on the safety profile of anthrax vaccine adsorbed, adjuvanted (AV7909; CYFENDUS). Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) or Post-Marketing Commitments (PMCs) are warranted, or if a Risk Evaluation and Mitigation Strategy (REMS) is required for AV7909, should the product be approved. Please refer to Appendix 1 for a list of materials reviewed for this memorandum.

2 BACKGROUND

Anthrax is an infectious disease caused by *Bacillus anthracis*, which occurs naturally and commonly affects domestic and wild animals [1]. Clinical manifestations in humans can include cutaneous, inhalational, gastrointestinal, and injection anthrax [1]. Without treatment, inhalation anthrax is almost always fatal. However, with aggressive treatment, about 55% of patients survive [1]. Because *B. anthracis* can persist as a spore, it is considered a serious biological threat as a potential weapon [2].

3 PRODUCT INFORMATION

3.1 Product Description

Per the proposed package insert (PI):

CYFENDUS vaccine is a sterile, milky-white suspension for IM injection and consists of AVA formulated with CPG 7909 adjuvant, a Toll-like receptor 9 agonist....

*AVA, which is formulated to contain the same ingredients as the licensed BioThrax vaccine, is made from cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *B. anthracis*. The production cultures are grown in a chemically defined protein-free medium consisting of a mixture of amino acids, vitamins, inorganic salts, and sugars. AVA contains proteins, including the 83 kDa protective antigen (PA) protein, released during the growth period, and contains no dead or live bacteria. AVA proteins, in the form of Anthrax Vaccine (AV) Filtrate, are adsorbed onto an aluminum hydroxide adjuvant and formulated by suspending into a saline preservative solution containing the excipients sodium chloride, formaldehyde, benzethonium chloride, and water for injection...*

The final product is formulated to contain AVA (100 mcg/mL total adsorbed AV Filtrate, 1.3 mg/mL aluminum adjuvant, (b) (4) in 0.85% sodium chloride, with 25 mcg/mL benzethonium chloride and 100 mcg/mL formaldehyde added as preservatives) and 0.5 mg/mL CPG 7909 adjuvant.

...Each 0.5 mL dose of AV7909 contains (b) (4) of AVA and (b) (4) of CPG 7909, in 0.85% NaCl solution with formaldehyde and benzethonium chloride added as preservatives. The proposed dosing regimen for AV7909 is two doses (0.5 mL each) given two weeks apart administered via intramuscular injection (deltoid muscle) following suspected or confirmed *B. anthracis* exposure to individuals that are concomitantly receiving recommended antibacterial regimen.

3.2 Proposed Indication

Per the proposed PI: *CYFENDUS (Anthrax Vaccine Adsorbed, Adjuvanted)* is a vaccine 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 recommended antibacterial regimen.

OBPV defers to product office on the final language for the indication statement. Please see the final version of the PI submitted by the sponsor for the final agreed-upon indication after FDA review.

4 PERTINENT REGULATORY HISTORY

The Sponsor is seeking approval for AV7909 for use as a post-exposure prophylactic (PEP) vaccine 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.

Emergent developed AV7909 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 2/10/2016, FDA confirmed that this licensure strategy was appropriate for AV7909 for the PEP indication. AV7909 was granted Orphan Drug Designation (DRU-2021-8325) on 19 August 2021. Therefore, the Pediatric Research Equity Act (PREA) requirements do not apply.

AV7909 is not currently licensed or authorized in any country.

5 DESCRIPTION OF AV7909 CLINICAL TRIAL SAFETY DATA

The clinical study safety data reviewed are from the PVP and Summary of Clinical Safety submitted to BLA 125761.0. Below is our focused review of the Sponsor data to inform decisions pertaining to pharmacovigilance planning, should this vaccine be approved. OBPV defers to OVRP for final review of the clinical database, including safety and efficacy outcomes. Please refer to the PI for the final clinical safety data.

5.1 Clinical Studies

The integrated safety cohort includes 3,424 people from four studies (Table 1). The median age was 38 years (range 18-65), and 1,976 (57.7%) of subjects were female, including 1,386 (40.5%) women of child-bearing potential. Subject race was reported as Black (567; 16.6%), White (2,692; 78.6%) or other (165; 4.8%), and 2,891 (84.4%) individuals were non-Hispanic.

The integrated safety cohort includes subjects in dose-finding studies, but this review focuses on subjects who received the (b) (4) /formulation of AV7909 (i.e., AVA 0.5 mL + 0.25 mg CpG 7909 given IM at Week 0 and 2).

Table 1. Summary of clinical studies supporting the efficacy and safety of AVA7909*

Study	N	Description
AVA.201	integrated safety cohort: 17 total subjects: 105	Phase 1 dose selection study in healthy adults 18-50 years of age Randomized, parallel-arm, double-blind, placebo- and active-controlled To evaluate safety, tolerability, and immunogenicity of four AVA plus CPG 7909 (AV7909) formulations, compared to saline placebo and AVA alone local and systemic AEs through day 7, abnormal labs, diary
AVA.208	integrated safety cohort: 44 total subjects: 168	Phase 2 dose schedule-finding study in healthy adults 18-50 years of age Randomized, parallel-arm, double-blind, active-controlled To assess safety and immunogenicity of three vaccination schedules and two dose levels of AV7909 AEs through day 84, SAEs up to 1 year, solicited AEs through day 7, abnormal labs, immunologically significant AEs
AVA.210	integrated safety cohort: 64 total subjects: 210	Phase 2 antibacterial drug-vaccine interaction study in healthy adults 18-45 years of age Randomized, parallel-arm, open-label, active-controlled To evaluate pharmacokinetic profiles of ciprofloxacin and doxycycline, safety and AV7909 immunogenicity, when antibacterial drugs are co-administered with AV7909 AEs through day 51, SAEs up to 1 year. AESIs up to 1 year, abnormal labs, diary
AVA.212	integrated safety cohort: 3,299 total subjects: 3,862	Phase 3 pivotal safety, lot consistency, and immunogenicity study in healthy adults 18-65 years of age Randomized, parallel-arm, double-blind, active-controlled To demonstrate AV7909 lot consistency, immunogenicity under FDA's Animal Rule TNA NF50 threshold requirement at Day 64, noninferiority of AV7909 to BioThrax, and safety, after IM administration of two doses two weeks apart AEs through day 64, SAEs up to 1 year, autoimmune AESIs up to 1 year, abnormal labs, diary

*Adapted from Sponsor's PVP (Table 3).

5.2.1 Adverse Events - Overview

Table 2 summarizes adverse events in the safety subset, including TEAEs that led to discontinuation of vaccination or study withdrawal; deaths and other serious adverse events (SAEs); and adverse events of special interest (AESIs).

Overall, 3,173 (92.7%) of subjects experienced an AE (Table 2), but only 273 (8%) had severe reactions (Grade 3 or higher).

Of treatment-emergent adverse events (TEAEs) affecting at least 1% of subjects, the most common were injection site pain (4.6%), tiredness (3.7%), upper respiratory tract infection (3.1%), myalgia (2.9%), and headache (2.7%).

Solicited local reactions occurred in a large majority of people (3,142; 91.8%), with more than half of subjects reporting tenderness (87.2%), pain (85.3%), or limited arm mobility (62.7%) (not mutually exclusive). Warmth (49.7%), induration (36.5%), swelling (19.2%), and erythema (17.3%) were less common. Severe local reactions were uncommon (3.7%).

Solicited systemic adverse events were also common (2,841; 83.0% of subjects), with more than half of people experiencing myalgia (73.7%), fatigue (64.9%), or headache (55.6%) (not mutually exclusive). Nausea (11.8%) and fever (6.3%) were less common. Severe systemic reactions were infrequent (6.3%).

Table 2. Adverse events in the safety subset ^a

	Subjects N = 3,424 n ^b (%)
Any adverse event (AE)	3,173 (92.7)
Grade 3+	273 (8.0)
Any local AE	3,142 (91.8)
Grade 3+	125 (3.7)
Any systemic AE	2,841 (83.0)
Grade 3+	214 (6.3)
Treatment-emergent adverse event (TEAE)	1,339 (39.1)
	<i>498 (14.5)</i>
Grade 3+ TEAE	217 (6.3)
	<i>44 (1.3)</i>
TEAE leading to discontinuation of vaccination	78 (2.3)
TEAE leading to study withdrawal	2 (0.06)
Serious Adverse Event (SAE)	62 (1.8)
	<i>1 (0.03)</i>
Adverse Event of special interest (AESI)	15 (0.44)
	<i>3 (0.09)</i>
Death	6 (0.18)
	<i>0</i>

^a Adapted from Summary of Clinical Safety (Table 10a) and Integrated Summary of Safety Addendum (Table 11.1.10.2).

^b In each cell, numbers and percentages in plain text represent the total for that adverse event, and the italicized numbers represent adverse events that the investigator deemed to be related to AV7909.

Among subjects who received the (b) (4) /formulation of AV7909, there were six deaths. Two women and four men died, with age ranging from 24 to 55 years. Death occurred 1-255 days after the last vaccination. Three men died of suicide, one man died of an unintentional mitragynine overdose, one woman died of an unintentional heroin overdose, and one woman died of unknown causes 245 days after the last vaccination. Investigators deemed all six deaths to be unrelated to AV7909.

In addition, a 42-year-old man in study AVA.201 died due to a motor vehicle accident 345 days after the last dose of a formulation that will not be marketed (AVA 0.5 mL + CPG7909 0.5 mg). His death was considered unrelated to the investigational product.

Only 1.8% of subjects experienced SAEs, the most common of which was spontaneous abortion (5 cases; 0.1%).

Investigators considered one SAE to be possibly related to AV7909, described below.

Subject US(b) (6)

42-year-old woman developed cholecystitis 1 day after vaccination and, after a brief improvement followed by worsening symptoms/signs, she underwent cholecystectomy 5 days after vaccination. The event was considered resolved.

Reviewer comment: These results do not suggest any unexpected safety concerns. There are no concerning patterns in the clinical categories, frequency, severity, or onset time of AEs.

5.2.2 Adverse Events of Special Interest

Per the Sponsor:

Since there is a potential for CpG oligodeoxynucleotide adjuvants to trigger autoimmune disease in susceptible individuals, possibly as a result of non-specific activation of T- or B-lymphocytes, all study protocols included assessments for autoimmune reactions.

Any AEs associated with AV7909 use that might be manifestations of autoimmune disease were carefully monitored and were separately analyzed in AV7909 trials as adverse events of special interest.

A total of 15 adverse events of special interest (AESIs) occurred after AV7909 vaccination.

Endocrine (n=3)

Autoimmune thyroiditis (1 unrelated)

Graves-Basedow's (2 unrelated)

Gastrointestinal (n=2)

Celiac disease (1 unrelated)

Ulcerative colitis (1 possibly related; please see below)

Musculoskeletal and connective tissue (n=3)

Polymyalgia rheumatica (1 unrelated)

Psoriatic arthropathy (1 unrelated)

Systemic lupus erythematosus (1 unrelated)

Dermatologic (n=7)

Alopecia areata (1 unrelated)

Chronic spontaneous urticaria (1 possibly related; please see below)

Diffuse alopecia (1 possibly related; please see below)

Guttate psoriasis (2 unrelated)

Subacute cutaneous lupus (2 unrelated)

Three AESIs (all non-serious) were deemed possibly related to AV7909:

Subject US(b) (6)

43-year-old woman developed abdominal pain, bloating, cramping, hematochezia/diarrhea and fatigue and was diagnosed with ulcerative colitis 208 days after vaccination. Biopsies taken during colonoscopy revealed severe Mayo grade 3 ulcerative colitis throughout the entire colon, including chronic colitis with marked acute/active inflammation. She received treatment and is reportedly stable.

Subject US(b) (6)

32-year-old woman was diagnosed with chronic spontaneous urticaria 76 days after AV7909. Recovery status was not reported.

Subject US(b) (6)

57-year-old woman experienced diffuse alopecia 17 days after AV7909. Her hair grew back, and the event was considered resolved.

Reviewer comment: The total number of AESIs was small, and there was no conspicuous clustering. Among the three AESIs that were considered possibly related, there was no obvious pattern in signs/symptoms, and the onset intervals spanned a wide time range. DPV agrees that the other AESIs are likely not related to AV7909. DPV defers to OVRP for detailed review of clinical trial data.

5.2.3 Pregnancy

Pregnant women were excluded from the clinical trials for AV7909. Of 35 cases of inadvertent AV7909 vaccination during or before pregnancy (33 subjects; two twin pregnancies), 24 exposures occurred before pregnancy and the rest were during the first trimester. Outcomes included live births (23; 66%), spontaneous abortion (7; 20%), elective abortion (4; 11%), or fetal demise (1; 3%). Among the live births, two infants had congenital anomalies. One infant was born with pulmonary hyperplasia, bilateral renal aplasia, and hydrocephalus (major anomalies) resulting in death 24 hours after birth; these anomalies were considered unrelated to AV7909. One infant was born with a biliary cyst (major anomaly) and labial tie (minor anomaly), both of which were considered possibly related to vaccination. Among control subjects in the clinical trials for AV7909, pregnancy outcomes included: term delivery of healthy infant after saline placebo (1 case), term delivery of healthy infant after BioThrax (1), and spontaneous abortion after BioThrax (1).

Reviewer comment: Based on limited data regarding maternal and infant outcomes following AV7909 vaccination during pregnancy, it is difficult to draw any definitive conclusions.

6 SUMMARY OF POSTMARKETING EXPERIENCE

There is no postmarketing experience with AV7909.

Per the Sponsor's proposed PI, AV7909 "is formulated to contain the same ingredients as the licensed BioThrax vaccine [and] is made from cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *B. anthracis*." Therefore, the postmarketing safety experience with BioThrax is relevant.

6.1 Vaccine Adverse Event Reporting System (VAERS)

BioThrax has been used in the US military population for more than 50 years. From 1998 through 12/31/2022, approximately (b) (4) doses have been distributed in the US (approximately 16,698,369 administered). Routine postmarketing surveillance—including review of serious adverse event reports, data mining, periodic submissions from the manufacturer, and the medical literature—has not identified any changes in the safety profile of BioThrax in the past 10 years.

Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, stimulated reporting, variable report quality and accuracy, inadequate data regarding dosing, and lack of direct and unbiased comparison groups. VAERS reports may not be medically confirmed and are not always verified by FDA. Furthermore, there is no certainty that the reported event was actually due to the product.

6.2 Data Mining

As of 12/30/2022, Empirica Bayes data mining [3] for BioThrax identified $EB05 \geq 2$ [4] for 36 Preferred Terms (Appendix 2). FDA has published surveillance reviews of these AEs, among others [5,6]. Many of these signs and symptoms have been found to pertain to “multisystem illness” experienced by Gulf War veterans likely to have been vaccinated with BioThrax, defined as “chronic symptoms involving at least two of the following three categories: fatigue, mood-cognition, and musculoskeletal system” [7]. Vaccination site reactions have been reported after BioThrax and other injected vaccines. Myopericarditis is a known risk following concomitant smallpox vaccine. Cardiovascular signs and symptoms are relatively common among middle-aged adults of both sexes. Many service members are of reproductive age, and terms pertaining to pregnancy tests reflect the demographics of the target population. Finally, positive rechallenge is not an adverse event.

Data mining is subject to a number of limitations, including the limits of spontaneous surveillance systems described in the section above. There may be confounding by indication or false alerts from concomitant product administration. In addition, a signal may be reflected in multiple PTs that individually do not reach alert threshold.

6.3 Sponsor’s Periodic Reports

Emergent’s Periodic Benefit-Risk Evaluation Reports for BioThrax have not raised additional safety concerns.

6.4 BioThrax Pregnancy Registry

In the submission, the sponsor provided information on a postmarketing pregnancy registry for BioThrax. Since July 15, 2012, Emergent has voluntarily conducted a single arm, observational pregnancy registry for individuals who were vaccinated while pregnant or within 30 days of becoming pregnant. Study outcomes and endpoints are described below:

- Infant health outcomes: birth defects, infant sex ratio, preterm birth, and low birth weight
- Pregnancy outcomes: stillbirth, spontaneous abortion, elective termination, ectopic pregnancy, and molar pregnancy
- Maternal outcomes: maternal death, preeclampsia/eclampsia, preterm labor, and gestational diabetes
- Timing of vaccination and cumulative number of doses: potential associations with maternal and infant health outcomes

On August 9, 2018, FDA agreed with the Sponsor's proposal to close the registry. Through October 22, 2018 (close of enrollment), 98 women had consented. Of 91 women for whom follow-up information was available, there were 90 healthy infants and one ectopic pregnancy resulting in fetal loss. Other outcomes included preterm labor (10 cases), preterm birth (7), eclampsia/preeclampsia (7), gestational diabetes (7), and low birth weight (4). There were two major birth defects (gastroschisis and cleft palate) and one minor one (syndactyly). In addition, there was one case of imperforate anus in an infant whose parents were vaccinated before (not during) pregnancy. Investigators felt that the congenital anomalies and the ectopic pregnancy were unlikely to be related to anthrax vaccine.

Reviewer comment: The BioThrax pregnancy registry was intended to collect data prospectively regarding spontaneously reported exposures and maternal and infant outcomes, with no hypothesis testing. Enrollment was low, limiting meaningful analysis, and completing the registry as originally proposed was ultimately infeasible.

7 SPONSOR'S PHARMACOVIGILANCE PLAN

7.1 Pharmacovigilance - Overview

The Sponsor submitted a Pharmacovigilance Plan (PVP) based on pharmacological class effects. Table 3 summarizes Emergent's assessment of the risk specification and missing information for AV7909. The Sponsor's pharmacovigilance activities will include routine review of individual case safety reports, aggregate reports, signal detection, risk management activities, performance monitoring, inspections and audits, and pre- and postlicensure study management per 21 CFR 600.80.

Table 3. Sponsor’s Pharmacovigilance Plan

<p>Important Identified Risk: Anaphylaxis</p> <p>Hypersensitivity reactions may occur and anaphylaxis has been reported rarely.</p> <p><i>Routine risk minimization measures:</i> The risk of an anaphylactic reaction can be minimized by thorough patient screening prior to vaccination. As with all vaccines, providers who administer vaccines should have an emergency protocol and access to supplies to treat anaphylaxis. Observation following AV7909 should be consistent with each clinic’s protocol for all vaccines.</p> <p>Planned risk mitigation actions: Known risk to be followed up via routine pharmacovigilance activities through signal detection and adverse reaction reporting; safety labeling in Sections 4 and 5.</p> <p><i>Effectiveness Measurement:</i> Should the pharmacovigilance monitoring result in the identification of an increased signal, the signal will be evaluated and categorized, and a Signal Detection Benefit-Risk Assessment Report, including risk minimization and risk communication actions, will be prepared as defined in the company signal detection Standard Operating Procedure (SOP). Labeling changes and/or urgent safety restrictions will be introduced as appropriate.</p> <p><i>Evaluation/Reporting:</i> As per normal Periodic Safety Update Report (PSUR) data lock points. In addition, at any time point where a signal is identified following the receipt of a spontaneous adverse event.</p>
<p>Important Potential Risk: Injection site reactions in women</p> <p>There is an increased risk for injection site reactions in female recipients. Results for both overall and gender-specific reactogenicity are consistent with other anthrax safety studies. The age-adjusted relative risk for injection site reactions in women compared to men was 2.78 (95% CI: 2.29, 3.38).</p> <p>Planned Risk Mitigation Action: Ongoing monitoring with signal detection performed per SOP.</p>
<p>Important Potential Risk: Trauma to ulnar nerve</p> <p>Trauma to ulnar nerve is a direct nerve injury or local inflammatory response to vaccine. The risk increases if the vaccine is administered into the triceps muscle. Incidents of trauma to ulnar nerve are preventable and considered rare if the vaccine is administered with proper technique into the deltoid muscle.</p> <p>Planned Risk Mitigation Action: Ongoing monitoring with signal detection performed per SOP.</p>
<p>Important Potential Risk: Congenital anomalies</p> <p>A pregnancy registry (EBS.AVA.010) was initiated in 2012 to identify risk of adverse pregnancy, maternal health, and infant health, outcomes. In 2018, CBER concurred that the feasibility of collecting sufficient information had diminished due to an unacceptable level of enrollment, and agreed to discontinue regulatory tracking of the pregnancy registry.</p> <p>Planned Risk Mitigation Action: Ongoing monitoring with signal detection performed per SOP.</p>
<p>Important Potential Risk: Immune-mediated events</p> <p>Immune-mediated events / autoimmune events of special interest (e.g., ulcerative colitis, chronic idiopathic urticaria, malignancies of the immune system, monoclonal gammopathy, systemic lupus erythematosus, arthritis, and optic neuritis)</p> <p>AV7909, like all vaccines, induces protection by stimulating the recipient’s immune system. An enhanced or aberrant immune stimulation may manifest clinically as hypersensitivity, which may occur immediately after immunisation, or may be delayed for days or weeks following immunisation. These rare, delayed, immunologically-mediated adverse events are poorly understood, but are believed to possibly result from a number of immune mechanisms, including Type II, Type III, and Type IV hypersensitivity.</p> <p>Planned Risk Mitigation Action: Ongoing monitoring with signal detection performed per SOP.</p>

Important Potential Risk: Guillain-Barré syndrome (GBS)
BioThrax and AV7909 administration has not been associated with increases in the rate of GBS; however, such increases have been seen with other vaccines. GBS has been described to occur after immunization with BioThrax; however, this has not been above the expected background rate.
Planned Risk Mitigation Action: Ongoing monitoring with signal detection performed per SOP.
Important Potential Risk: Severe cutaneous reactions
Uncommon occurrence of severe reactions has been reported over the course of approximately 16.1 million BioThrax immunizations which suggests a minimal health impact.
Planned Risk Mitigation Action: Ongoing monitoring with signal detection performed per SOP.
Important Missing Information: Pregnant women or lactating mothers
There are no adequate and well-controlled studies of AV7909 vaccine in pregnant women. AV7909 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Planned Risk Mitigation Actions: Ongoing monitoring with signal detection performed per SOP, safety labeling in sections 5.3, 8.1, and 8.2.
Important Missing Information: Pediatrics
The administration of AV7909 has not been studied in the pediatric population. Therefore, AV7909 should only be used when the benefit outweighs the risk.
Planned Risk Mitigation Actions: Ongoing monitoring with signal detection performed per SOP and safety labeling in section 8.4.
Important Missing Information: Geriatrics
AV7909 has been administered to persons ≥ 66 years of age as part of the B-SAFE study (BARDA elderly study), however the data are limited. The primary safety analyses in pooled age ≥ 66 years showed that the most common local AEs were injection site pain, tenderness, warmth, and erythema. Fatigue, myalgia, and headache were the most common systemic AEs observed in aged ≥ 66 . Therefore, AV7909 should only be used when the benefit outweighs the risk.
Planned Risk Mitigation Actions: Ongoing monitoring with signal detection performed per SOP and safety labeling in section 8.5.
Important Missing Information: Impaired immune responsiveness
The administration of AV7909 has not been studied in the subjects with impaired immune responsiveness. Subjects with impaired immune responsiveness due to congenital, acquired immunodeficiency, or immunosuppressive therapy may have reduced antibody responses to active immunization.
Planned Risk Mitigation Actions: Ongoing monitoring with signal detection performed per SOP and safety labeling in Section 5.2.
Important Missing Information: People exposed to <i>Bacillus anthracis</i> spores
The administration of AV7909 has not been studied in subjects exposed to <i>Bacillus anthracis</i> spores
Planned Risk Mitigation Action: Ongoing monitoring with signal detection performed per SOP.

7.2 Proposed Postmarketing Study

In addition to routine pharmacovigilance, Emergent has submitted a protocol synopsis for a postmarketing study (“Phase 4 Retrospective Observational Study of AV7909 Anthrax Vaccine Post-exposure Prophylaxis Following a *Bacillus Anthracis* Mass Exposure Event”; EBS-AVA-213) to evaluate the clinical benefit and safety of AV7909. The study would be performed as a PMR under regulations for products approved under the Animal Rule, 21 CFR 601.91(b)(1). The study, which is expected to last at least 12 months after containment of the outbreak, will be considered completed based on case review of up to 250 confirmed cases of inhalational anthrax and/or anthrax meningitis, or vaccination of up to 10,000 individuals who also received the recommended antibacterial drugs.

Safety assessments will include AEs, SAEs, pregnancy outcomes, and fetal anomalies, including medical record review for individuals who are hospitalized for suspected or confirmed inhalational anthrax and/or anthrax meningitis, as well as safety data collected during the mass exposure event (VAERS, spontaneous reports to the manufacturer, and the literature).

The sponsor proposes the following milestones for the study:

- Final Protocol Submission: 3/31/2024
- Study/Trial Completion: to be determined should an event occur
- Final Report Submission: to be determined should an event occur

8 KEY SAFETY-RELATED PRODUCT LABELING

The draft PI includes the following language:

In Section 5, Warnings and Precautions:

5.3 Pregnancy

CYFENDUS can cause fetal harm when administered to a pregnant individual. In an observational study there was a numerical imbalance in birth defects, with more observed in infants born to individuals vaccinated with BioThrax (a licensed anthrax vaccine with the same active ingredient as CYFENDUS) in the first trimester compared to individuals vaccinated outside of the first trimester. BioThrax does not contain CPG 7909 adjuvant.

If CYFENDUS is administered during pregnancy, the vaccinated individual should be apprised of the potential hazard to a fetus [see Use in Specific Populations (8.1)].

Section 6.2, Postmarketing Experience:

There is no postmarketing experience following administration of CYFENDUS. However, the postmarketing safety experience with BioThrax is relevant since the vaccines are manufactured similarly and contain the same antigens.

The following additional adverse events have been spontaneously reported during the postmarketing use of BioThrax and may occur in people receiving CYFENDUS. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Adverse events included below are listed due to one or more of the following factors: The reports included below are listed due to one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug to BioThrax.

Blood and lymphatic system disorders: Lymphadenopathy

Gastrointestinal Disorders: Nausea

Immune system disorders: Allergic reactions (including anaphylaxis, angioedema, rash, urticaria, pruritus, erythema multiforme, anaphylactoid reaction, and Stevens-Johnson syndrome)

Nervous system disorders: Paresthesia, syncope, dizziness, tremor, ulnar nerve neuropathy

Musculoskeletal, connective tissue, and bone disorders: Arthralgia, arthropathy, myalgia, rhabdomyolysis, alopecia

General Disorders and Administration Site Conditions: Malaise, pain, cellulitis, flu-like symptoms

Psychiatric disorders: Insomnia

Skin and Subcutaneous Tissue Disorders: Pruritis, rash, urticaria

Vascular disorders: Flushing

Infrequent reports of the following were also received: multisystem disorder defined as chronic symptoms involving at least two of the following three categories: fatigue, mood-cognition, and musculoskeletal system.

Section 8, Use In Specific Populations:

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In clinically recognized pregnancies in the US general population, the estimated background risk of major birth defects is 2% to 4% and of miscarriage is 15% to 20%.

There are no adequate and well-controlled studies of CYFENDUS in pregnant individuals.

Available human data on CYFENDUS administered to pregnant individuals do not establish the presence or absence of vaccine-associated risks in pregnancy (see Human Data).

Data are available from a BioThrax observational study and pregnancy exposure registry. BioThrax is a licensed anthrax vaccine with the same active ingredient as CYFENDUS. BioThrax does not contain CPG 7909 adjuvant. In the observational study there was a numerical imbalance in birth defects, with more birth defects in infants born to individuals vaccinated with BioThrax in the first trimester compared to individuals vaccinated outside of the first trimester or individuals never vaccinated with BioThrax. Data from the BioThrax pregnancy exposure registry do not establish the presence or absence of vaccine-associated risks in pregnancy (see Human Data).

Data

Human Data

In pre-licensure clinical studies of CYFENDUS, women underwent pregnancy testing immediately prior to administration of each dose of CYFENDUS. Despite this pregnancy screening regimen, some subjects (n=11) were vaccinated with CYFENDUS very early in pregnancy before human chorionic gonadotropin (HCG) was detectable. Twenty-two subjects with 24 pregnancies (two twin pregnancies) were exposed to CYFENDUS prior to conception. Of the 35 pregnancies reported in CYFENDUS-vaccinated women, 7 (20%) resulted in miscarriage and there were 2 infants (5.7%) born with major birth defects.

Available data in pregnant women are not sufficient to determine the effects of CYFENDUS on pregnancy, embryo-fetal development, parturition and postnatal development.

A pregnancy exposure registry was conducted in individuals who received BioThrax, a vaccine with the same active ingredient as CYFENDUS. Of 91 individuals who reported pregnancy outcomes, the majority of exposures were in the first trimester (n=89), and adverse pregnancy outcomes included two infants with major birth defects, one fetal loss (ectopic pregnancy) and seven premature births. In addition, a large observational study examined the rate of birth defects among 37,140 infants born to US military service personal who received BioThrax vaccine during pregnancy between 1998 and 2004. Birth defects were slightly more common in first trimester-exposed infants 4.68% when compared with infants 4.15% of individuals vaccinated outside of the first trimester (odds ratio = 1.18; 95% confidence interval: 0.997, 1.41) or when compared to individuals never vaccinated with BioThrax (odds ratio = 1.20; 95% confidence interval: 1.02, 1.42).

Reviewer comment: Regarding Postmarketing Experience, the included text is derived directly from Section 6.2 of BioThrax vaccine; inclusion of this summary of adverse events that have been reported after BioThrax is warranted, given the similarity of the two products with respect to important risks and missing information (Appendix 3).

Regarding pregnancy/lactation, it is appropriate to include available data for both AV7909 and BioThrax. A small number of people were vaccinated with AV7909 during or before pregnancy, and data are therefore limited. Original data from the observational study of BioThrax are not available, but the language that Emergent has proposed for 8.1 is consistent with the published results [8]. The summary of information from the BioThrax pregnancy registry reflects the data submitted by the sponsor. DPV agrees with the proposed language in

8.1, but defers to OVRP for a final determination. Please see the final version of the PI submitted by the sponsor for the final agreed-upon indication after FDA review.

9 ANALYSIS OF SPONSOR'S PVP AND PROPOSED STUDY

9.1 Analysis of PVP

The Sponsor's PVP adequately reflects the safety concerns based on clinical trial experience with AV7909, as well as postmarketing experience with BioThrax.

9.2 Analysis of Proposed Postmarketing Study

In the event of a public health emergency, use of AV7909 in the general population might reveal adverse events that were not observed during the clinical trials. In the PMR study, Emergent will collect information about pregnancy/fetal outcomes. A separate pregnancy registry for AV7909 will not be feasible, as AV7909 is intended for use in a PEP scenario and not active (pre-exposure) immunization. The study that Emergent is proposing for AV7909 is similar to the one which the company proposed as a PMR for BioThrax PEP.

Although the indication proposed in this BLA specifies vaccination with concomitant antimicrobial therapy, during an emergency people might deviate from the approved indication and public health officials may revise their recommendations. DPV will defer to DB regarding statistical methods for analyzing subgroups with differential exposure to antimicrobials.

10 DPV ASSESSMENT AND RECOMMENDATIONS

The safety data from four clinical trials of AV7909 revealed that the vaccine was generally well-tolerated. The important risks and important missing information for AV7909 are similar to those for BioThrax, which—based on decades of experience in the US military population—has been demonstrated to be generally safe. Should AV7909 be approved, the Sponsor's proposed plans for conducting a required postmarketing study (safety-related PMR under FDAAA Title IX) and routine pharmacovigilance and AE reporting in accordance with 21 CFR 600.80 [7] are adequate for monitoring postmarketing safety. The PMR registry study will further evaluate the clinical benefit and safety of AV7909. The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy. The proposed PVP is adequate.

Please see the final version of the PI submitted by the sponsor for the final agreed-upon language for the label.

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Appendix 1 – Materials Reviewed

- Clinical overview
- Summary of Clinical Safety
- Clinical study reports and individual study synopses
- Integrated summary of safety, including Major Amendment
- Pharmacovigilance Plan (PVP), original and revised
- Draft PI
- Responses to Information Requests (please see below)

DPV requested additional information from the Sponsor (please see table) and found the responses to be adequate:

Information Request		Amendment / Response
IR #7 8/10/2022	Asked manufacturer to clarify pharmacovigilance activities for pregnant/lactating women	Amendment #10 8/17/2022 Contains updated PVP to include pharmacovigilance activities for pregnant/lactating women
IR #4 7/7/2022 #14 10/12/2022	Requested subject narratives, BioThrax comparator, and sensitivity analyses excluding data from site US1027	Amendment #27 11/18/2022 Contains updated clinical overview, summary of clinical safety, clinical study reports, integrated summary of safety (including BioThrax as comparator), and draft PI; includes responses to IRs
IR #20 12/19/2022	Asked manufacturer to clarify pharmacovigilance activities for potential risks	Amendment #33 1/25/2023 Contains updated PVP to include pharmacovigilance activities for injection site reactions in women, trauma to ulnar nerve, and congenital anomalies
IR #29 4/13/2023	Requested final protocol submission date for Phase 4 PMR Field Study	Amendment #46 4/20/2023 For the Phase 4 PMR Field study, the Sponsor will submit the final study protocol by 3/31/2024. Emergent acknowledges that the dates for study completion and submission of the final study report determined should an anthrax emergency event occur.
IR #33 5/26/2023	Requested additional pregnancy data; asked manufacturer to propose additional language in package insert (8.1)	Amendment #55 6/8/2023 Contains additional information about timing (trimester) of exposure; includes updated draft package insert with additional language about pregnancy data for BioThrax

Appendix 2 - Data Mining Results

As of 12/30/2022, (b) (4) for BioThrax revealed EB05 \geq 2 for the following Preferred Terms:

Affect lability
Amnesia
Arthralgia
Blood cholesterol increased
Bone pain
Chronic fatigue syndrome
Depression
Disturbance in attention
Dyspnoea exertional
Eczema
Fibromyalgia
Gastroesophageal reflux disease
Human chorionic gonadotropin increased
Human chorionic gonadotropin negative
Human chorionic gonadotropin positive
Hypertension
Hypothyroidism
Injection site pruritus
Insomnia
Irritable bowel syndrome
Memory impairment
Migraine
Mood swings
Nodule
Osteoarthritis
Post-traumatic stress disorder
Pustule
Rheumatoid factor negative
Skin lesion
Skin tightness
Sleep disorder
Troponin I increased
Troponin T increased
Vaccination site swelling
Vaccine positive rechallenge
Weight increased

Appendix 3 - Important risks and missing information as noted in the PVPs for BioThrax and AV7909

	Important Identified Risk	Important Potential Risk	Important Missing Information
Anaphylaxis	BioThrax; AV7909		
Injection site reactions in women	BioThrax	AV7909	
Trauma to ulnar nerve	BioThrax	AV7909	
Congenital anomalies	BioThrax	AV7909	
Immune-mediated events		BioThrax; AV7909	
Guillain-Barré syndrome		BioThrax; AV7909	
Severe cutaneous reactions		BioThrax; AV7909	
Pregnant women or lactating mothers			BioThrax; AV7909
Pediatrics			BioThrax; AV7909
Geriatrics			BioThrax; AV7909
Impaired immune responsiveness			BioThrax; AV7909
People exposed to <i>Bacillus anthracis</i> spores			BioThrax; AV7909

*Adapted from Sponsor Tables 10-13 in PVP Version 4.