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Review Completion Date / Stamped Date	
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Applicant	Emergent Product Development Gaithersburg, Inc.
Established Name	Anthrax Vaccine Adsorbed, Adjuvanted
(Proposed) Trade Name	CYFENDUS
Dosage Form(s) and Route(s) of Administration	Suspension for Intramuscular Injection
Dosing Regimen	Two 0.5 mL doses, two weeks apart
Indication(s) and Intended Population(s)	For post-exposure prophylaxis of disease following suspected or confirmed exposure to <i>Bacillus anthracis</i> in persons 18 through 65 years of age when administered in conjunction with the recommended antibacterial regimen

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GLOSSARY

ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area Under Curve
AVA	Anthrax Vaccine Adsorbed
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BMI	Body Mass Index
CBER	Center for Biologics Evaluation and Research
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
IM	Intramuscular
ISS	Integrated Summary of Safety
FAS	Full Analysis Set
MAAE	Medically Attended Adverse Event
NF50	50% Neutralizing Factor
PK	Pharmacokinetic
PP	Per-Protocol
SAE	Serious Adverse Event
SDTM	Study Data Tabulation Model
TNA	Toxin-Neutralizing Antibody
VE	Vaccine Efficacy

1. EXECUTIVE SUMMARY

Emergent initiated a rolling Biologics License Application (BLA) on December 14, 2021 (STN 1257610) to seek licensure of CYFENDUS (Anthrax Vaccine Adsorbed, Adjuvanted; hereafter referred to as AV7909) under the Animal Rule for post-exposure prophylaxis (PEP) 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. AV7909 consists of the Anthrax Vaccine Adsorbed (AVA) drug substance (DS) and the CPG 7909 adjuvant, where the AVA DS is made with the same ingredients, (b) (4), and using (b) (4) manufacturing process as the AVA DS contained in BioThrax, a licensed vaccine indicated for active immunization for the prevention of disease caused by *Bacillus anthracis* in persons 18 to 65 years of age at high risk of exposure as both pre- and post-exposure prophylaxis. This BLA submission for AV7909 was completed on April 20, 2022. Due to extensive changes to the study datasets to address issues identified during review, which were submitted under STN 125761/0.15 on September 9, 2022 and resulted in revisions to the original safety results, the amendment was designated as Major.

This BLA is supported by safety and immunogenicity data from Studies EBS.AVA.201, EBS.AVA.208, EBS.AVA.210, and EBS.AVA.212. Studies EBS.AVA.201 and EBS.AVA.208 were Phase 1 and Phase 2 dose selection studies, respectively. Therefore, this review focuses on Studies EBS.AVA.210 and EBS.AVA.212 and the integrated analysis of safety (ISS) for the four studies. Due to data integrity issues identified at Site #1027 in Study EBS.AVA.212, all results presented in this review exclude data from this site.

Study EBS.AVA.210 was a Phase 2, randomized, open-label, multicenter trial to investigate potential interactions of AV7909 vaccination with ciprofloxacin or doxycycline when administered concomitantly. A total of 210 participants 18 to 45 years of age were randomized in a 1:1:1 ratio to receive AV7909 and ciprofloxacin, AV7909 and doxycycline, or AV7909 alone. The first 40 participants in the two coadministration groups underwent pharmacokinetic (PK) assessments prior to and after AV7909 vaccination. All participants were evaluated for immune responses to AV7909 in terms of the Toxin-Neutralizing Antibody (TNA) assay 50% neutralizing factor (NF50) titers. 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 coadministered with ciprofloxacin or doxycycline were noninferior (via a 2-fold margin) to the immune responses to AV7909 administered alone.

Equivalence of ciprofloxacin steady-state PK parameters prior to vs. after AV7909 coadministration was met in terms of the area under curve (AUC_{0-12h}; Geometric Mean Ratio [GMR] = 0.98; 90% Confidence Interval [CI]: 0.89 to 1.07) and maximum concentration (C_{max}; GMR = 0.97; 90% CI: 0.87 to 1.08). Equivalence of doxycycline steady-state PK parameters prior to vs. after AV7909 coadministration was met for

AUC_{0-12h} (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). The NF50 GMT in the AV7909/ciprofloxacin coadministration group was noninferior to that of the AV7909 single administration group (GMR = 1.13; 95% CI = 0.78 to 1.64). In the AV7909/doxycycline coadministration group, the GMR was 1.14 with 95% CI 0.81 to 1.60.

Study EBS.AVA.212 was a Phase 3, randomized, double-blind trial to evaluate the lot consistency, immunogenicity, and safety of AV7909 in healthy adults 18 to 65 years of age under a PEP indication. A total of 3689 participants were randomized in a 2:2:2:1 ratio to receive one of three consecutive lots of AV7909 (Groups 1 – 3) or BioThrax (Group 4). Participants were vaccinated on Day 1, Day 15, and Day 29, with those randomized to AV7909 receiving placebo on Day 29 to maintain blinding. The primary objectives were to demonstrate AV7909 lot consistency based on the Day 64 NF50 geometric mean titers (GMTs) via a 2-fold equivalence margin and superiority to 40% in terms of the percentages of participants achieving Day 64 NF50 ≥ 0.56 in each lot, and noninferiority to BioThrax via a -15% margin in terms of the percentages of participants achieving Day 64 NF50 ≥ 0.29 . The secondary objective was to demonstrate superiority to 67% in terms of the percentage of AV7909 participants achieving Day 29 NF50 ≥ 0.15 .

Lot consistency based on Day 64 NF50 GMTs was demonstrated. Among participants who received AV7909, 66.3% (95% CI: 64.4% to 68.1%) achieved Day 64 NF50 ≥ 0.56 . In addition, AV7909 was noninferior to BioThrax in terms of the percentage of participants achieving Day 64 NF50 ≥ 0.29 (difference [AV7909 minus BioThrax] = 25.2%; 95% CI: 20.5% to 30.1%). Based on data from the nonhuman primates (NHP) challenge Study 3655-100072763 and the immune responses observed among AV7909 recipients, the Predicted Vaccine Efficacy (PVE) of AV7909 was 96.8% (95% CI: 92.4% to 98.9%) on Day 29 and 82.9% (95% CI: 55.1% to 96.7%) on Day 64.

As for safety, the most commonly reported reactions after vaccination with AV7909 were tenderness, pain, and muscle ache, with most being mild or moderate in severity. Compared with BioThrax, frequencies of local reactions after AV7909 vaccination were similar or lower except for arm motion limitation, while frequencies of systemic reactions were generally higher. A numerically lower frequency of unsolicited adverse events (AEs) in Study EBS.AVA.212 was observed among AV7909 recipients compared with BioThrax recipients, while numerically higher frequencies of serious AEs (SAEs) and deaths were observed among AV7909 recipients. There was no notable difference in the percentages of participants reporting any AE of special interest (AESI).

In conclusion, two intramuscular (IM) doses of AV7909 given two weeks apart elicits noninferior immune responses compared to three subcutaneous (SC) doses of BioThrax. Vaccination with AV7909 does not appear to meaningfully interfere with ciprofloxacin PK, but equivalence was not demonstrated with respect to doxycycline PK. In addition, data suggest no notable interference on the immune response to AV7909 after coadministration with ciprofloxacin or doxycycline.

I defer to the clinical reviewer on the overall safety conclusion.

2. CLINICAL AND REGULATORY BACKGROUND

BioThrax is a licensed vaccine indicated for active immunization for the prevention of disease caused by *Bacillus anthracis* in persons to 18 to 65 years of age at high risk of exposure as both pre- and post-exposure prophylaxis. Emergent initiated a rolling BLA on December 14, 2021 (STN 125761/0) to seek licensure of CYFENDUS (AV7909), which consists of the AVA contained in BioThrax and the CPG 7909 adjuvant, under the Animal Rule for PEP 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. The BLA submission was completed on April 20, 2022. Due to extensive changes to the study datasets to address issues identified during review, which were submitted under STN 125761/0.15 on September 9, 2022 and resulted in revisions to the original safety results, the amendment was designated as Major.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The applicant made a number of revisions to the Standard Data Tabulation Model (SDTM) datasets for Studies EBS.AVA.210 and EBS.AVA.212 to address database issues identified during review. These revisions included the transfer of solicited reactions that did not continue past Day 7 from the AE to the CE datasets, the addition of solicited reactions to the AE datasets that continued beyond Day 7, and the addition of key information that were missing in the CE datasets from the original submission.

The revised datasets resulted in changes to the safety summaries for the studies and the ISS. Due to the extensive changes made during review, the amendment containing the majority of these revisions (STN 125761/0.15) was designed as Major.

3.2 Compliance With Good Clinical Practices And Data Integrity

Systemic issues related to data integrity and Good Clinical Practice (GCP) compliance during the conduct of Study EBS.AVA.212 were identified at Site #1027 in the United States. Key inspections findings by Emergent and QualityHub are summarized below:

- Errors in height measurement conversions and inconsistencies between participant-reported heights and their corresponding database values.
- Modifications to the source vital signs records by the study coordinator that may have led to the enrollment of ineligible participants.
- Adverse events occurring during study participation found in the electronic medical records were not reported in the participant record files for multiple participants.
- Concomitant medications prescribed/taken during the study by several participants were not documented in the participant record files, some of which may have been protocol deviations.
- Subjects meeting exclusion criteria for certain medical history may have been inappropriately enrolled due to oversight.

- Date of concomitant medication use reported by one participant during screening was modified by site staff, potentially to avoid study exclusion.

Due to the questionable integrity of data obtained from Site #1027, all immunogenicity and safety results presented in this review exclude data from Site #1027. Please refer to Haecin Chun's Bioresearch Monitoring (BIMO) inspections review memo for details of the BIMO inspection.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

Please refer to reviews by other review disciplines.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This statistical review focuses on the immunogenicity and safety data from Studies EBS.AVA.210 and EBS.AVA.212 and the ISS from Studies EBS.AVA.201, EBS.AVA.208, EBS.AVA.210, and EBS.AVA.212.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

Information from the following amendments submitted to STN 125761/0 were reviewed:

1. Amendment 3 (submitted on 4/20/22)
2. Amendment 4 (submitted on 6/16/22)
3. Amendment 6 (submitted on 7/19/22)
4. Amendment 7 (submitted on 7/20/22)
5. Amendment 15 (submitted on 9/9/22)
6. Amendment 17 (submitted on 9/19/22)
7. Amendment 19 (submitted on 9/23/22)
8. Amendment 20 (submitted on 9/28/22)
9. Amendment 22 (submitted on 10/5/22)
10. Amendment 27 (submitted on 11/18/22)
11. Amendment 31 (submitted on 12/20/22)
12. Amendment 38 (submitted on 2/28/23)

5.3 Table of Studies/Clinical Trials

Studies conducted to support the PEP indication of AV7909 are summarized in Table 1 below.

Table 1. Clinical Studies Supporting the BLA

Study	Description	Total Randomized
EBS.AVA.201	Phase 1, parallel-arm, double-blind, randomized, placebo-controlled, dose-ranging study to evaluate the safety, tolerability, and	0.5 mL AVA: 18 0.5 mL AVA + 0.5 mg CPG: 18 0.5 mL AVA + 0.25 mg CPG: 17 0.25 mL AVA + 0.5 mg CPG: 19

Study	Description	Total Randomized
	immunogenicity of AV7909 in adults 18 to 50 years of age	0.25 mL AVA + 0.25 mg CPG: 18 Placebo: 15
EBS.AVA.208	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	AV7909 (Days 1, 15): 44 AV7909 (Days 1, 29): 34 AV7909 (Days 1, 15, 29): 23 Half dose AV7909 (Days 1, 15, 29): 44 BioThrax (Days 1, 15, 29): 23
EBS.AVA.210	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	AV7909 + ciprofloxacin: 70 AV7909 + doxycycline: 71 AV7909: 69
EBS.AVA.212	Phase 3, randomized, double-blind study in adults 18 to 65 years of age to evaluate the safety, lot consistency, and immunogenicity of AV7909	AV7909 (Lot 1): 1053 AV7909 (Lot 2): 1054 AV7909 (Lot 3): 1049 BioThrax: 553

BioThrax dose = 0.5 mL AVA; AV7909 dose = 0.5 mL AVA + 0.25 mg CPG.

Source: Summarized by the reviewer based on information provided in the ISS Addendum.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study EBS.AVA.210

6.1.1 Objectives

Primary Objective:

- To evaluate the pharmacokinetic (PK) profiles of ciprofloxacin or doxycycline when administered orally prior to and following the intramuscular (IM) administration of a two-dose schedule of AV7909 administered two weeks apart.

Secondary Objectives:

- To assess the safety of concurrent administration of oral ciprofloxacin or doxycycline and two doses of AV7909 administered IM.
- To evaluate the Day 37 immune response using the toxin-neutralizing antibody (TNA) assay following two IM doses of AV7909 with and without the concurrent oral administration of ciprofloxacin or doxycycline.

6.1.2 Design Overview

Study EBS.AVA.210 was a Phase 2, randomized, open-label, multicenter trial to investigate the potential interactions of AV7909 vaccination with ciprofloxacin or doxycycline when administered concomitantly. A total of 210 participants were to be randomized in a 1:1:1 ratio to receive AV7909 and ciprofloxacin concomitantly (Group 1), AV7909 and doxycycline concomitantly (Group 2), or AV7909 only (Group 3).

Participants in Group 1 were administered orally with one dose of ciprofloxacin every 12 hours from Day 4 to Day 9, Day 22 to Day 24, and Day 31 to Day 37. Participants in Group 2 were administered orally with one dose of doxycycline every 12 hours from Day 2 to Day 9, Day 22 to Day 24, and Day 32 to Day 38. All participants received AV7909 on Day 8 and Day 23.

The first 40 subjects randomized to Group 1 underwent PK assessments on Days 4, 8, 31, and 35 (Group 1a) and the first 40 subjects randomized to Group 2 underwent PK assessments on Days 2, 8, 32, and 38 (Group 2a). On PK assessment days, blood samples for drug concentrations were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours after the morning dose.

For all participants, blood samples for TNA assessments were collected on Day 1 and Day 37. Solicited local and systemic reactions were assessed for at least seven days after each vaccination. AEs, SAEs, and AESIs were collected up to Day 388.

6.1.3 Population

The study population consisted of healthy adults 18 through 45 years of age.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study interventions included AV7909 (0.5 mL AVA + 0.25 mg CPG 7909) administered IM, and ciprofloxacin (500 mg) and doxycycline (100 mg) administered orally.

6.1.6 Sites and Centers

A total of four sites in the United States participated in the study.

6.1.7 Surveillance/Monitoring

Please refer to Dr. Alexandra Worobec's clinical review memo.

6.1.8 Endpoints and Criteria for Study Success

Primary PK Endpoints

1. Area under curve from 0 to 12 hours (AUC_{0-12h}) and maximum concentration (C_{max}) for Ciprofloxacin on Days 8 and 35.
2. AUC_{0-12h} and C_{max} for doxycycline on Days 8 and 38.

For each antibiotic, to conclude that AV7909 coadministration does not affect the steady state PK profile, the two-sided 90% CIs for the geometric means of the within-participant ratios of the post-vaccination (Day 35 for ciprofloxacin and Day 38 for doxycycline) over the pre-vaccination (Day 8) values are within [0.8, 1.25] for both AUC_{0-12h} and C_{max} .

Secondary PK Endpoints

1. AUC_{0-12h} and C_{max} for ciprofloxacin on Days 4 and 31.

2. AUC_{0-12h} and C_{max} for doxycycline on Days 2 and 32.

No hypothesis was evaluated for the secondary PK endpoints. The 90% CIs for the geometric means of the within-participant ratios of the post-vaccination (Day 31 for ciprofloxacin and Day 32 for doxycycline) over the pre-vaccination (Day 4 for ciprofloxacin and Day 2 for doxycycline) values for both AUC_{0-12h} and C_{max} are presented for information on interference with single-dose PK parameters.

Secondary Immunogenicity Endpoints

1. TNA NF50 on Day 37.

For each antibiotic, to conclude that antibiotic coadministration does not affect the immune response to AV7909, the lower bound of the two-sided 95% CI for the GMR of TNA NF50 values at Day 37 (Group 1 over Group 3 for ciprofloxacin and Group 2 over Group 3 for doxycycline) must be greater than 0.5.

Safety Endpoints

1. Incidence of solicited systemic and injection site reactions following each vaccination.
2. Incidence of AEs through Day 51.
3. Incidence of SAEs through Day 388.
4. Incidence of AESIs through Day 388.
5. Incidence of clinical laboratory abnormalities.

No hypothesis was evaluated for the safety endpoints.

6.1.9 Statistical Considerations & Statistical Analysis Plan

PK analyses were based on the PK Population, defined as participants in Groups 1a and 2a who received two doses of AV7909 according to protocol, received at least 5 of the 7 in-clinic ciprofloxacin doses between Days 4 to 8 and Days 31 to 35 or at least 7 of the 9 in-clinic doxycycline doses between Days 2 to 8 and Days 32 to 38, had adequate data for calculation of the PK parameters on Day 8 and Day 35 (Group 1a) or Day 38 (Group 2a), and had no major protocol deviations.

Immunogenicity analyses were based on the Immunogenicity Population, defined as all randomized participants who received two doses of AV7909 according to protocol, had valid TNA result on Day 1 with NF50 less than the limit of detection of 0.059, had valid TNA result on Day 37 with sample collected within the appropriate time window, and for Groups 1 and 2, took at least 50% of the protocol-specified antibiotic doses.

The two-sided 90% CIs for the geometric means of the within-participant ratios for AUC_{0-12h} and C_{max} were calculated based on the t-distribution of the mean of the log-transformed values and exponentiating the mean. The two-sided 95% CI for the NF50 GMR was calculated based on a linear regression of the log-transformed NF50 titers with

group as the independent variable. NF50 titers below the Lower Limit of Quantitation (LLOQ) were imputed with LLOQ/2.

Multiplicity was not adjusted for tests across antibiotics. For each antibiotic, the primary PK objective was met if equivalence was demonstrated for both steady state AUC_{0-12h} and C_{max}. Noninferiority of immune responses to AV7909 was evaluated only if the primary PK objective was met for that antibiotic.

Safety endpoints were summarized descriptively by computing the number and percentage of participants in the Safety Population who reported at least one event, where the Safety Population consisted of all randomized participants who received at least one dose of the antibiotic or AV7909. Participants were analyzed according to the intervention received.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 2 shows the disposition of the randomized population. A total of 210 participants were randomized, approximately 90% of whom received at least one dose of the study vaccine or antibiotic. The percentage of participants included in the Immunogenicity Population was slightly higher in Group 3 (78.3%) than in Groups 1 (67.1%) and 2 (70.4%).

Table 2. Participant Disposition

-	AV7909 + Cipro Group 1a n (%)	AV7909 + Cipro Group 1 n (%)	AV7909 + Doxy Group 2a n (%)	AV7909 + Doxy Group 2 n (%)	AV7909 Only Group 3 n (%)
Randomized/Assigned	45	70	45	71	69
Treated	41 (91.1)	62 (88.6)	42 (93.3)	64 (90.1)	64 (92.8)
Completed Day 51 Visit	33 (73.3)	53 (75.7)	39 (86.7)	59 (83.1)	61 (88.4)
Safety Population	41 (91.1)	62 (88.6)	42 (93.3)	64 (90.1)	64 (92.8)
PK Population	25 (55.6)	-	31 (68.9)	-	-
Immunogenicity Population	28 (62.2)	47 (67.1)	36 (80.0)	50 (70.4)	54 (78.3)

Source: Adapted from Tables 12 and 14 of EBS.AVA.210 Clinical Study Report.

6.1.10.1.1 Demographics

Table 3 presents the demographic characteristics of the Safety Population. Overall, baseline characteristics with respect to age, sex, race, and ethnicity were similar between treatment arms. Demographic characteristics of the PK and Immunogenicity Populations (not shown) were similar to the Safety Population.

Table 3. Demographics – Safety Population

-	AV7909 + Cipro Group 1a N=41 n (%)	AV7909 + Cipro Group 1 N=62 n (%)	AV7909 + Doxy Group 2a N=42 n (%)	AV7909 + Doxy Group 2 N=64 n (%)	AV7909 Only Group 3 N=64 n (%)
Age (Years)	-	-	-	-	-
Mean (Std Dev)	33.0 (8.0)	32.7 (7.5)	31.0 (7.7)	32.3 (7.9)	32.3 (8.1)
Median (Min, Max)	34 (19, 45)	34 (19, 45)	32 (18, 44)	34 (18, 44)	33 (20, 45)
Sex	-	-	-	-	-
Female	28 (68.3)	41 (66.1)	28 (66.7)	41 (64.1)	39 (60.9)
Male	13 (31.7)	21 (33.9)	14 (33.3)	23 (35.9)	25 (39.1)
Race	-	-	-	-	-
White	27 (65.9)	43 (69.4)	22 (52.4)	37 (57.8)	46 (71.9)
Black/African American	12 (29.3)	16 (25.8)	18 (42.9)	25 (39.1)	16 (25.0)
Other/More than One Race	2 (4.9)	3 (4.8)	2 (4.8)	2 (3.1)	2 (3.1)
Ethnicity	-	-	-	-	-
Not Hispanic/Latino	36 (87.8)	54 (87.1)	38 (90.5)	57 (89.1)	55 (85.9)
Hispanic/Latino	5 (12.2)	8 (12.9)	3 (7.1)	6 (9.4)	9 (14.1)
Not Reported	0	0	1 (2.4)	1 (1.6)	0

Source: Table 14.1.4.2 of EBS.AVA.210 Clinical Study Report.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Table 4 presents the equivalence assessments of ciprofloxacin (Group 1a) and doxycycline (Group 2a) steady-state PK parameters in the PK population. The primary objective of demonstrating equivalence of ciprofloxacin steady-state PK parameters prior to vs. after AV7909 coadministration was met for both AUC_{0-12h} (GMR = 0.98; 90% CI: 0.89 to 1.07) and C_{max} (GMR = 0.97; 90% CI: 0.87 to 1.08). The primary objective of demonstrating equivalence of doxycycline steady-state PK parameters prior to vs. after AV7909 coadministration was met for AUC_{0-12h} (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).

Table 4. Equivalence of Steady-State PK Parameters – PK Population

Antibiotic	Time Points	Parameter	n	GMR	90% CI
Ciprofloxacin	Day 35 vs. Day 8	AUC _{0-12h}	25	0.98	(0.89, 1.07)
Ciprofloxacin	Day 35 vs. Day 8	C _{max}	25	0.97	(0.87, 1.08)
Doxycycline	Day 38 vs. Day 8	AUC _{0-12h}	30	0.92	(0.82, 1.03)
Doxycycline	Day 38 vs. Day 8	C _{max}	31	0.90	(0.78, 1.03)

n = number of non-missing pairs.

Source: Adapted from Tables 21 and 24 of EBS.AVA.210 Clinical Study Report.

Reviewer Comment:

- All analyses presented in this review were confirmed based on data submitted in the SDTM format, and the results were consistent with those reported by the applicant.

6.1.11.2 Analyses of Secondary Endpoints

Table 5 presents the descriptive measures of ciprofloxacin (Group 1a) and doxycycline (Group 2a) single-dose PK parameters in the PK population. The within-participant GMRs (post- vs. pre-AV7909 coadministration) of ciprofloxacin single-dose PK parameters were 0.93 for AUC_{0-12h} (90% CI = 0.79 to 1.10) and 0.95 for C_{max} (90% CI: 0.79 to 1.13). The within-participant GMRs (post- vs. pre-AV7909 coadministration) of doxycycline single-dose PK parameters were 1.05 for AUC_{0-12h} (90% CI: 0.86 to 1.28) and 1.01 for C_{max} (90% CI: 0.82 to 1.24).

Table 5. Equivalence of Single-Dose PK Parameters – PK Population

Antibiotic	Time Points	Parameter	n	GMR	90% CI
Ciprofloxacin	Day 31 vs. Day 4	AUC _{0-12h}	24	0.93	(0.79, 1.10)
Ciprofloxacin	Day 31 vs. Day 4	C _{max}	24	0.95	(0.79, 1.13)
Doxycycline	Day 32 vs. Day 2	AUC _{0-12h}	26	1.05	(0.86, 1.28)
Doxycycline	Day 32 vs. Day 2	C _{max}	26	1.01	(0.82, 1.24)

n = number of non-missing pairs.

Source: Adapted from Tables 21 and 24 of EBS.AVA.210 Clinical Study Report.

Table 6 presents the noninferiority assessments of the Day 37 immune responses to AV7909 coadministered with ciprofloxacin or doxycycline compared to AV7909 administered alone. Noninferiority of NF50 titers was demonstrated in the ciprofloxacin coadministration group (GMR = 1.13; 95% CI = 0.78 to 1.64). In the doxycycline coadministration group, GMR was 1.14 with 95% CI 0.81 to 1.60.

Table 6. Comparison of Day 37 AV7909 Immune Responses – Immunogenicity Population

Group	Treatments	n	GMT (95% CI)	GMR (95% CI)
1	AV7909 + Ciprofloxacin	47	1.80 (1.33, 2.45)	1.13 (0.78, 1.64)
2	AV7909 + Doxycycline	50	1.81 (1.41, 2.33)	1.14 (0.81, 1.60)
3	AV7909 Only	54	1.59 (1.26, 2.01)	Reference

n = number of participants in the Immunogenicity Population.

Source: Adapted from Tables 26 and 28 of EBS.AVA.210 Clinical Study Report.

Reviewer Comment:

- As the doxycycline coadministration group failed the overall primary PK objective, noninferiority of Day 37 NF50 titers was not tested and results are presented descriptively for this group.

6.1.11.3 Subpopulation Analyses

Subgroup analyses of Day 37 NF50 titers are presented in Table 7 by age group and sex for each treatment arm. Overall, Day 37 NF50 GMTs in coadministration Groups 1 and 2 were generally similar to the single administration Group 3 in each subgroup.

Table 7. Day 37 NF50 Titers by Age Group and Sex – Immunogenicity Population

	AV7909 + Cipro Group 1 n, GMT (95% CI)	AV7909 + Doxy Group 2 n, GMT (95% CI)	AV7909 Only Group 3 n, GMT (95% CI)
Age Group	-	-	-
18-30 Years	19, 2.4 (1.7, 3.5)	18, 1.9 (1.2, 2.9)	24, 1.7 (1.3, 2.4)
31-45 Years	28, 1.5 (0.9, 2.3)	32, 1.8 (1.3, 2.5)	30, 1.5 (1.0, 2.1)
Sex	-	-	-
Female	32, 1.9 (1.3, 2.6)	33, 1.7 (1.2, 2.5)	34, 1.4 (1.0, 1.9)
Male	15, 1.7 (0.8, 3.5)	17, 2.0 (1.5, 2.6)	20, 1.9 (1.3, 2.8)

n = number of participants in the Immunogenicity Population.

Source: Adapted from Tables 14.2.2.4 and 14.2.2.5 of EBS.AVA.210 Clinical Study Report.

6.1.12 Safety Analyses

Table 8 presents the numbers and percentages of participants who reported any local or systemic reaction within 7 days of any injection. The most commonly reported reactions in all arms 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, while the percentage reporting any systemic reaction was slightly lower in the AV7909/ciprofloxacin coadministration arm.

Table 8. Solicited Local and Systemic Reactions within 7 Days of Any Dose – Safety Population

	AV7909 + Cipro N=58 Any n (%)	AV7909 + Cipro N=58 Grade ≥3 n (%)	AV7909 + Doxy N=59 Any n (%)	AV7909 + Doxy N=59 Grade ≥3 n (%)	AV7909 Only N=64 Any n (%)	AV7909 Only N=64 Grade ≥3 n (%)
Injection Site Reaction	47 (81.0)	1 (1.7)	51 (86.4)	1 (1.7)	55 (85.9)	5 (7.8)
Arm Motion Limitation	30 (51.7)	0	34 (57.6)	0	38 (59.4)	0
Bruising	6 (10.3)	0	7 (11.9)	1 (1.7)	11 (17.2)	1 (1.6)
Induration	22 (37.9)	0	30 (50.8)	0	26 (40.6)	3 (4.7)
Itching	13 (22.4)	0	21 (35.6)	1 (1.7)	18 (28.1)	0
Pain	41 (70.7)	0	45 (76.3)	1 (1.7)	54 (84.4)	2 (3.1)
Erythema/Redness	14 (24.1)	1 (1.7)	16 (27.1)	0	17 (26.6)	2 (3.1)
Swelling	14 (24.1)	1 (1.7)	18 (30.5)	0	16 (25.0)	2 (3.1)
Tenderness	44 (75.9)	0	50 (84.7)	1 (1.7)	54 (84.4)	0
Warmth	30 (51.7)	0	28 (47.5)	1 (1.7)	32 (50.0)	0
Systemic Reaction	40 (69.0)	1 (1.7)	49 (83.1)	1 (1.7)	48 (75.0)	8 (12.5)
Tiredness	29 (50.0)	1 (1.7)	39 (66.1)	1 (1.7)	38 (59.4)	4 (6.3)
Headache	24 (41.4)	1 (1.7)	32 (54.2)	0	36 (56.3)	6 (9.4)
Muscle Ache	35 (60.3)	1 (1.7)	40 (67.8)	0	45 (70.3)	3 (4.7)
Fever	2 (3.4)	1 (1.7)	0	0	5 (7.8)	3 (4.7)

N = number of vaccinated participants in the Safety Population who reported any e-diary data.

n = number of participants reporting the event.

Source: Adapted from Tables 14.3.4.9.1b and 14.3.4.9.2b submitted to STN 125761/0.31.

The percentages of participants who reported any AE after the first vaccine or antibiotic dose up to the end of follow-up on Day 388 in each arm are shown in Table 9. A slightly higher percentage of participants administered with both AV7909 and ciprofloxacin reported any AE compared with those administered with AV7909 alone, while the percentages of participants reporting AEs considered by the investigator to be related to any study treatment were similar among treatment arms. Two participants across the three arms reported any SAE, but none were considered related to the study treatment by the investigator. No deaths or AESIs were reported during the study.

Table 9. Summary of Unsolicited AEs – Safety Population

	AV7909 + Cipro N=62 n (%)	AV7909 + Doxy N=64 n (%)	AV7909 Only N=64 n (%)
AEs	32 (51.6)	29 (45.3)	28 (43.8)
Related to any treatment	16 (25.8)	17 (26.6)	15 (23.4)
Related to antibiotic only	6 (9.7)	7 (10.9)	0
Related to vaccine only	11 (17.7)	12 (18.8)	15 (23.4)
Related to both antibiotic and vaccine	0	1 (1.6)	0
Grade ≥ 3 AEs	6 (9.7)	6 (9.4)	4 (6.3)
Related to any treatment	1 (1.6)	0	3 (4.7)
Related to antibiotic only	0	0	0
Related to vaccine only	1 (1.6)	0	3 (4.7)
Related to both antibiotic and vaccine	0	0	0
SAEs	1 (1.6)	0	1 (1.6)
Related to any treatment	0	0	0
Deaths	0	0	0
AEs leading to discontinuation of any treatment	2 (3.2)	1 (1.6)	0
AEs leading to discontinuation of vaccine	1 (1.6)	0	0
AEs leading to discontinuation of antibiotic	1 (1.6)	1 (1.6)	0
AEs leading to study withdrawal	1 (1.6)	0	0
AESIs	0	0	0

N = number of participants in the Safety Population.

n = number of participants reporting the event.

Source: Table 14.3.1.1a submitted to STN 125761/0.38.

Reviewer Comments:

- *In the Clinical Study Report, non-treatment-emergent AEs from two participants were erroneously included in the AE summaries. These events were removed in a subsequent re-analysis per CBER request, which is reflected in this review.*
- *The percentages of participants who reported any AE up to Day 51, the secondary safety endpoint, did not suggest a notable difference in pattern among groups.*

6.2 Study EBS.AVA.212

6.2.1 Objectives

Primary Objective:

- To demonstrate lot consistency following a two-dose schedule of AV7909 administered IM in healthy adults.
- To demonstrate immunogenicity under the Animal Rule on Day 64 following a two-dose schedule of AV7909 administered IM in healthy adults.
- To demonstrate immunogenicity using the Animal Rule on Day 64 based on the noninferiority of a two-dose schedule of AV7909 administered IM to the licensed three-dose schedule of BioThrax administered SC in healthy adults.
- To evaluate the safety of AV7909 in healthy adults following a two-dose schedule administered IM.

Secondary Objectives:

1. To demonstrate immunogenicity under the Animal Rule on Day 29 following a two-dose schedule of AV7909 administered IM in healthy adults.

6.2.2 Design Overview

Study EBS.AVA.212 was a Phase 3, randomized, double-blind, active-control, multicenter trial to evaluate the lot consistency, immunogenicity, and safety of AV7909 in healthy adults 18 to 65 years of age under a PEP indication. A total of 3850 participants were to be randomized in a 2:2:2:1 ratio to receive one of three consecutive lots of AV7909 (Groups 1 – 3) or BioThrax (Group 4). Participants were vaccinated on Day 1, Day 15, and Day 29, with those randomized to AV7909 receiving placebo on Day 29 to maintain blinding.

Blood samples for immunogenicity testing were collected on Day 1, Day 29, and Day 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.

6.2.3 Population

The study population consisted of healthy adults 18 through 65 years of age.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The study interventions included AV7909 (0.5 mL AVA + 0.25 mg CPG 7909) administered IM and BioThrax (0.5 mL AVA) administered SC.

6.2.6 Sites and Centers

A total of 35 sites in the United States participated in the study.

6.2.7 Surveillance/Monitoring

As described in Section 3.2, systemic issues related to data integrity were identified at Site #1027 in the United States during the conduct of Study EBS.AVA.212. All immunogenicity and safety results presented in this review exclude data from Site #1027. Please refer to Dr. Alexandra Worobec's clinical review memo.

6.2.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoints

1. TNA NF50 on Day 64.
2. Percentage of participants achieving TNA NF50 ≥ 0.56 on Day 64.
3. Percentage of participants achieving TNA NF50 ≥ 0.29 on Day 64.

Lot consistency would be demonstrated if both of the following criteria were met: 1a) the 95% CI for the GMR of Day 64 TNA NF50 was within 0.5 to 2.0 for each of the three pairwise lot-to-lot comparisons among Groups 1 – 3, and 1b) the lower bound of the two-sided 95% CI was $\geq 40\%$ for the percentage of participants achieving Day 64 TNA NF50 ≥ 0.56 in each of the three lots (Groups 1 – 3).

The immunogenicity and noninferiority of AV7909 compared to BioThrax would be respectively demonstrated if the following criteria were met: 2a) the lower bound of the two-sided 95% CI was $\geq 40\%$ for the percentage of participants achieving Day 64 TNA NF50 ≥ 0.56 in the three AV7909 lots combined (Groups 1 – 3), and 2b) the lower bound of the two-sided 95% CI for the difference (AV7909 lots combined minus BioThrax) in the percentages of participants achieving Day 64 TNA NF50 ≥ 0.29 was $> -15\%$.

According to the applicant, the NF50 threshold values of 0.56 and 0.29 were based on 70% survival in rabbits and NHPs, respectively, after vaccination with BioThrax and challenge with *Bacillus Anthracis*.

Secondary Immunogenicity Endpoints

1. Percentage of participants achieving TNA NF50 ≥ 0.15 on Day 29.

The secondary immunogenicity objective would be demonstrated if: 3) the lower bound of the two-sided 95% CI was $\geq 67\%$ for the percentage of participants achieving Day 29 TNA NF50 ≥ 0.15 in the three AV7909 lots combined (Groups 1 – 3). According to the applicant, the NF50 threshold value of 0.15 was based on 70% survival in NHPs after vaccination with AV7909 and challenge with *Bacillus Anthracis*.

Safety Endpoints

1. Incidence of solicited systemic and injection site reactions following each vaccination.
2. Incidence of AEs through Day 64.
3. Incidence of SAEs through Day 394.
4. Incidence of AESIs through Day 394.
5. Incidence of clinical laboratory abnormalities.

No hypothesis was evaluated for the safety endpoints.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The two-sided 95% CIs for the Day 64 NF50 GMR between lots were calculated based on a linear regression of the log-transformed NF50 titers with lot as the independent variable. The between-lot differences in the mean log titers and their associated 95% CIs were back-transformed to obtain the GMRs and corresponding 95% CIs. For the percentages of participants achieving an NF50 threshold, the 95% CIs were calculated using the Clopper-Pearson method. The 95% CI for the difference in the percentages of participants achieving an NF50 threshold between AV7909 and BioThrax was calculated using the Newcombe score method. Titers below LLOQ were imputed with LLOQ/2. Hypotheses were evaluated sequentially as follows: 1a → 1b → 2a → 2b → 3.

Predicted vaccine efficacy (PVE) of AV7909 at Day 64 was evaluated as an exploratory analysis. PVE was defined as $PVE = \frac{p_u - p_v}{p_u}$ where p_u was the mean survival probability among unvaccinated individuals which was assumed to be 1, and p_v was the estimated mean survival probability among vaccinated individuals, estimated for each individual i by $p_v = \frac{1}{n} \sum_{i=1}^n \frac{1}{1 + \exp(-x_i)}$, where x_i was the Day 64 NF50 titer for the i^{th} AV7909 recipient, and α and β were the estimated intercept and slope of the logistic regression model for the logit of the survival probability after challenge on Day 70 on the Day 70 pre-challenge NF50 titer estimated from NHPs vaccinated with two doses of AV7909 in the NHP challenge Study 3655-100072763. PVE at Day 29 was estimated in a similar fashion based on the Day 29 NF50 titers and estimated logistic regression parameters from NHPs bled and challenged at Day 28 in the same challenge study. The 95% CIs for PVE were estimated based on a double-bootstrap method.

Immunogenicity and PVE analyses were based on the Per-Protocol (PP) Population, defined as all randomized participants who received the correct doses of the randomized vaccine within the appropriate time window, had valid TNA result on Day 1 with NF50 less than the limit of detection, had valid TNA result on Day 64 with sample collected within the appropriate time window, and had no other major protocol deviations.

Safety endpoints were summarized descriptively by computing the number and percentage of participants in the Safety Population who reported at least one event, where the Safety Population consisted of all randomized participants who received at least one dose of the vaccine. Participants were analyzed according to the intervention received.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Table 10 shows the disposition of the randomized population excluding Site #1027. A total of 3689 participants were randomized, of whom ≥99.7% in each arm received at least one dose of the study vaccine. The percentages of participants included in the PP Population were similar between arms (79.3% to 81.4%).

Table 10. Participant Disposition

-	AV7909 Lot 1 n (%)	AV7909 Lot 2 n (%)	AV7909 Lot 3 n (%)	AV7909 Pooled n (%)	BioThrax n (%)
Randomized	1053	1054	1049	3156	533
Treated	1050 (99.7)	1053 (99.9)	1048 (99.9)	3151 (99.8)	533 (100)
1 Vaccination	92 (8.7)	79 (7.5)	80 (7.6)	251 (8.0)	40 (7.5)
2 Vaccinations	59 (5.6)	53 (5.0)	57 (5.4)	169 (5.4)	21 (3.9)
3 Vaccinations	899 (85.4)	921 (87.4)	911 (86.8)	2731 (86.5)	472 (88.6)
Completed 12-month safety follow-up	984 (93.4)	977 (92.7)	987 (94.1)	2948 (93.4)	512 (96.1)
Safety Population	1050 (99.7)	1053 (99.9)	1048 (99.9)	3151 (99.8)	533 (100)
Per-Protocol Population	835 (79.3)	854 (81.0)	854 (81.4)	2543 (80.6)	430 (80.7)

Source: Adapted from Tables 1 and 3 of EBS.AVA.212 Clinical Study Report Addendum 2.

6.2.10.1.1 Demographics

Table 11 presents the demographic characteristics of the PP Population. Overall, baseline characteristics with respect to age, sex, race, and ethnicity were balanced between treatment arms. Demographic characteristics of the Safety Population (not shown) were similar to the PP Population.

Table 11. Demographics – PP Population

-	AV7909 Lot 1 N=835 n (%)	AV7909 Lot 2 N=854 n (%)	AV7909 Lot 3 N=854 n (%)	AV7909 Pooled N=2543 n (%)	BioThrax N=430 n (%)
Age (Years)	-	-	-	-	-
Mean (Std Dev)	39.6 (13.1)	39.2 (13.1)	39.4 (12.9)	39.4 (13.0)	38.8 (12.3)
Median (Min, Max)	39 (18, 65)	38 (18, 65)	38 (18, 65)	38 (18, 65)	37 (18, 64)
Sex	-	-	-	-	-
Female	495 (59.3)	474 (55.5)	502 (58.8)	1471 (57.8)	233 (54.2)
Male	340 (40.7)	380 (44.5)	352 (41.2)	1072 (42.2)	197 (45.8)
Race	-	-	-	-	-
White	664 (79.5)	666 (78.0)	657 (76.9)	1987 (78.1)	345 (80.2)
Black/African American	132 (15.8)	150 (17.6)	150 (17.6)	432 (17.0)	66 (15.3)
Other/More than One Race	39 (4.7)	38 (4.4)	47 (5.5)	124 (4.9)	19 (4.4)
Ethnicity	-	-	-	-	-
Not Hispanic/Latino	691 (82.8)	728 (85.2)	743 (87.0)	2162 (85.0)	352 (81.9)
Hispanic/Latino	132 (15.8)	118 (13.8)	101 (11.8)	351 (13.8)	70 (16.3)
Unknown	4 (0.5)	2 (0.2)	7 (0.8)	13 (0.5)	4 (0.9)
Not Reported	8 (1.0)	6 (0.7)	3 (0.4)	17 (0.7)	4 (0.9)

Source: Table 14.1.4.3b of EBS.AVA.212 Clinical Study Report Addendum 2.

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The Day 64 NF50 GMTs for AV7909 Lots 1 – 3 were 0.76 (95% CI: 0.72 to 0.81), 0.74 (95% CI: 0.70 to 0.79), and 0.72 (95% CI: 0.67 to 0.76), respectively. Lot consistency results based on the NF50 GMRs and percentages of participants with NF50 ≥ 0.56 on Day 64 are shown in Tables 12 and 13, respectively.

The primary objective of lot consistency was demonstrated, as the 95% CIs for the GMRs of Day 64 NF50 GMTs were within 0.5 to 2.0 for all three pairwise comparisons, and the lower bounds of the two-sided 95% CIs for the percentages of participants achieving Day 64 NF50 titer ≥ 0.56 were $\geq 40\%$ in all three lots. In addition, 66.3% (95% CI: 64.4% to 68.1%) of AV7909 recipients pooled across the three lots achieved Day 64 NF50 ≥ 0.56 , meeting the primary immunogenicity objective (2a).

Table 12. Lot Consistency Based on Day 64 NF50 GMR – PP Population

-	Lot 1 / Lot 2	Lot 1 / Lot 3	Lot 2 / Lot 3
GMR (95% CI)	1.03 (0.94, 1.13)	1.07 (0.98, 1.17)	1.04 (0.95, 1.13)

Source: Tables 6 of EBS.AVA.212 Clinical Study Report Addendum 2.

Table 13. Lot Consistency Based on Percentage with Day 64 NF50 ≥ 0.56 – PP Population

-	AV7909 Lot 1	AV7909 Lot 2	AV7909 Lot 3	AV7909 Pooled
n/N	575/835	560/854	550/854	1685/2543
% (95% CI)	68.9 (65.6, 72.0)	65.6 (62.3, 68.8)	64.4 (61.1, 67.6)	66.3 (64.4, 68.1)

N = number of participants in the PP Population.

n = number of participants achieving the threshold.

Source: Table 7 of EBS.AVA.212 Clinical Study Report Addendum 2.

The primary noninferiority objective (2b) comparing AV7909 and BioThrax in terms of the percentage of participants achieving Day 64 NF50 ≥ 0.29 was met, as the lower bound of the two-sided 95% CI for the difference in percentages (difference = 25.2%; 95% CI: 20.5% to 30.1%) was $> -15\%$ (Table 14).

Table 14. Day 64 Immune Responses by Arm – PP Population

-	AV7909 Pooled N=2543	BioThrax N=430
GMT (95% CI)	0.74 (0.71, 0.77)	0.33 (0.30, 0.36)
NF50 ≥ 0.29 , n (%; 95% CI)	2203 (86.6; 85.2, 87.9)	264 (61.4; 56.6, 66.0)
Difference, % (95% CI)	25.2 (20.5, 30.1)	Reference

n = number of participants achieving the threshold.

Source: Adapted from Tables 8 and 9 of EBS.AVA.212 Clinical Study Report Addendum 2.

Reviewer Comment:

- As a sensitivity analysis, inclusion of immunogenicity data from Site #1027 did not affect the lot consistency and immunogenicity conclusions.

6.2.11.2 Analyses of Secondary Endpoints

Out of 2491 AV7909 recipients in the PP Population who had a valid NF50 titer at Day 29, 2437 (97.8%; 95% CI: 97.2% to 98.4%) achieved a Day 29 NF50 titer ≥ 0.15 , meeting the secondary immunogenicity objective (3).

6.2.11.3 Subpopulation Analyses

Table 15 presents the proportions of participants achieving NF50 titer ≥ 0.56 on Day 64 by age group and sex. Overall, a higher percentage of participants with NF50 titer ≥ 0.56 on Day 64 was observed among AV7909 recipients compared to BioThrax recipients regardless of age and sex. Generally, a higher percentage of younger participants achieved Day 64 titer ≥ 0.56 . A higher percentage of female BioThrax recipients achieved a titer ≥ 0.56 on Day 64 compared to male participants, while the percentages were similar between female and male AV7909 recipients.

Table 15. Day 64 Immune Responses by Age Group and Sex – PP Population

	AV7909 NF50 ≥ 0.56 n/N (%)	BioThrax NF50 ≥ 0.56 n/N (%)
Age Group	-	-
18-30 Years	637/800 (79.6)	54/132 (40.9)
31-50 Years	677/1105 (61.3)	54/209 (25.8)
51-65 Years	371/638 (58.2)	26/89 (29.2)
Sex	-	-
Female	995/1471 (67.6)	92/233 (39.5)
Male	690/1072 (64.4)	42/197 (21.3)

N = number of participants in the PP Population.

n = number of participants achieving the threshold.

Source: Adapted from Tables 12 and 13 of EBS.AVA.212 Clinical Study Report Addendum 2.

6.2.11.5 Exploratory and Post Hoc Analyses

Estimated PVE at Day 29 and Day 64 based on data from the NHP challenge Study 3655-100072763 are presented in Table 16. Among AV7909 recipients in the PP Population, the estimated PVE was 96.8% (95% CI: 92.4% to 98.9%) on Day 29 and 82.9% (95% CI: 55.1% to 96.7%) on Day 64.

Table 16. PVE of AV7909 by Time Point – PP Population

Time Point	N	GMT	PVE % (95% CI)
Day 29	2491	1.49	96.8 (92.4, 98.9)
Day 64	2543	0.74	82.9 (55.1, 96.7)

N = number of AV7909 participants in the PP Population with valid NF50 titer.

Source: Table 11 of EBS.AVA.212 Clinical Study Report Addendum 2.

6.2.12 Safety Analyses

Table 17 presents the numbers and percentages of participants who reported any local or systemic reaction within 7 days of any injection, including placebo. The most commonly reported reactions among AV7909 recipients were tenderness (88.1%), pain (86.3%), and

muscle ache (75.2%). Frequencies of local reactions were similar or higher among BioThrax recipients than among AV7909 recipients except for arm motion limitation, while frequencies of systemic reactions were generally higher among AV7909 recipients.

Table 17. Solicited Local and Systemic Reactions within 7 Days of Any Dose – Safety Population

	AV7909 N=3106 Any n (%)	AV7909 N=3106 Grade ≥3 n (%)	BioThrax N=527 Any n (%)	BioThrax N=527 Grade ≥3 n (%)
Injection Site Reaction	2889 (93.0)	119 (3.8)	500 (94.9)	24 (4.6)
Arm Motion Limitation	1977 (63.7)	53 (1.7)	271 (51.4)	2 (0.4)
Bruising	533 (17.2)	9 (0.3)	184 (34.9)	0
Induration	1165 (37.5)	9 (0.3)	398 (75.5)	6 (1.1)
Itching	681 (21.9)	13 (0.4)	310 (58.8)	4 (0.8)
Pain	2680 (86.3)	66 (2.1)	463 (87.9)	5 (0.9)
Erythema/Redness	555 (17.9)	28 (0.9)	284 (53.9)	10 (1.9)
Swelling	613 (19.7)	12 (0.4)	292 (55.4)	7 (1.3)
Tenderness	2735 (88.1)	53 (1.7)	474 (89.9)	4 (0.8)
Warmth	1590 (51.2)	21 (0.7)	362 (68.7)	1 (0.2)
Systemic Reaction	2625 (84.3 ¹)	206 (6.6 ¹)	414 (78.4 ²)	20 (3.8 ²)
Tiredness	2083 (67.1)	89 (2.9)	283 (53.7)	9 (1.7)
Headache	1802 (58.0)	99 (3.2)	251 (47.6)	11 (2.1)
Muscle Ache	2335 (75.2)	110 (3.5)	334 (63.4)	10 (1.9)
Fever	211 (6.8 ³)	21 (0.7 ³)	9 (1.7)	2 (0.4)

N = number of participants in the Safety Population who reported any e-diary data.

n = number of participants reporting the event.

¹Based on a total of 3115 participants who reported any data.

²Based on a total of 528 participants who reported any data.

³Based on a total of 3113 participants who reported any data.

Source: Adapted from Tables 14.3.4.10.1b and 14.3.4.10.2b submitted to STN 125761/0.38.

Reviewer Comments:

- The Clinical Study Report did not appear to include summaries of onset and duration for the solicited reactions. Based on my calculations, among AV7909 recipients, the median study day of onset for each reaction was Day 1 to Day 3 and lasted for a median duration of 1 to 3 days.
- In the Clinical Study Report, solicited reactions from five subjects were attributed to incorrect dose number. However, this does not appear to impact the overall frequencies after any dose.
- The applicant calculated the percentages of participants reporting any solicited reaction based on the entire Safety Population regardless of whether any e-diary data for that participant were submitted. This implicitly assumes that participants who did not submit e-diary data did not experience any reaction. However, as the occurrence of solicited reactions for these participants is unknown, such assumption may potentially lead to under-reporting of the true frequency. Thus, the percentages were revised to reflect only those who provided e-diary data.

The percentages of participants who reported any AE up to Day 394 in each arm are shown in Table 18. A higher percentage of BioThrax recipients reported any AE, including AEs assessed by the investigator to be related to the study vaccine, compared with AV7909 recipients. A total of 58 (1.8%) AV7909 recipients and 4 (0.8%) BioThrax recipients reported any SAE, of whom 1 participant in each arm reported an SAE that was considered related to study vaccination by the investigator, including one AV7909 recipient who reported cholecystitis acute 19 days after the second AV7909 dose (5 days after the third dose with placebo). A total of 6 deaths were reported in the 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.

Table 18. Summary of Unsolicited AEs – Safety Population

	AV7909 N=3151 n (%)	BioThrax N=533 n (%)
AEs	1216 (38.6)	251 (47.1)
Related	453 (14.4)	169 (31.7)
Grade ≥ 3	204 (6.5)	29 (5.4)
Related Grade ≥ 3	41 (1.3)	8 (1.5)
Day 1 to Day 64	961 (30.5)	221 (41.5)
SAEs	58 (1.8)	4 (0.8)
Related	1 (<0.1)	1 (0.2)
Deaths	6 (0.2)	0
Related	0	0
AEs leading to discontinuation of vaccination	70 (2.2)	13 (2.4)
AEs leading to study withdrawal	1 (<0.1)	0
AESIs	15 (0.5)	2 (0.4)
Related	3 (0.1)	1 (0.2)

N = number of participants in the Safety Population.

n = number of participants reporting the event.

Source: Table 14.3.1.1b submitted to STN 125761/0.38.

Reviewer Comments:

- *In the Clinical Study Report, non-treatment-emergent AEs from eight participants were erroneously included in the AE summaries. These events were removed in a subsequent re-analysis per CBER request, which is reflected in this review.*
- *While data from Site #1027 were excluded in the AE summaries, no SAEs or AESIs were reported from this site.*

7. INTEGRATED OVERVIEW OF EFFICACY

No integrated analysis of efficacy was performed.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Frequencies of solicited local and systemic reactions and unsolicited AEs, SAEs, and AESIs reported after vaccination were summarized for the pooled safety data from each Safety Population across the studies. The following groups are considered in this review:

1. Participants who received at least one dose of AV7909 with the (b) (4) formulation, i.e. (b) (4) CPG 7909 given two weeks apart, excluding those coadministered with ciprofloxacin or doxycycline.
2. Participants who received BioThrax SC.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The studies contributing to the integrated summary are as follows:

1. EBS.AVA.201 – Phase 1 study where adults 18 to 50 years of age received two IM doses of: 1) 0.5 mL AVA, 2) 0.5 mL AVA + 0.5 mg CPG 7909, 3) 0.5 mL AVA + 0.25 mg CPG 7909, 4) 0.25 mL AVA + 0.5 mg CPG 7909, 5) 0.25 mL AVA + 0.25 mg CPG 7909, or 6) placebo two weeks apart.
2. EBS.AVA.208 – Phase 2 study where adults 18 to 50 years of age received via IM route: 1) two doses of AV7909 two weeks apart, 2) two doses of AV7909 four weeks apart, 3) three doses of AV7909 on Day 1, Day 15, and Day 29, 4) three half-doses of AV7909 on Day 1, Day 15, and Day 29, or 5) three doses of BioThrax on Day 1, Day 15, and Day 29.
3. EBS.AVA.210 – Phase 2 study as described in Section 6.1.
4. EBS.AVA.212 – Phase 3 study as described in Section 6.2.

The (b) (4) AV7909 formulation consisted of Study EBS.AVA.201 Group 3 (n=17), Study EBS.AVA.208 Group 1 (n=44), participants who received AV7909 only in Study EBS.AVA.210 (n=64), and participants who received any lot of AV7909 in Study EBS.AVA.212 (n=3151). All participants who received BioThrax SC came from Study EBS.AVA.212 (n=533).

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Of the 3276 participants vaccinated with AV7909 at the to-be-marketed formulation, 3017 (92.1%) received both doses of the vaccine. Of the 533 BioThrax recipients, 21 (3.9%) received exactly two doses and 472 (88.6%) received all three doses of the vaccine. The demographics of the pooled Safety Population are shown in Table 19 by group. The distributions of age, sex, race, and ethnicity were similar between groups. The median age was 38 years in each group, with the majority being female.

Table 19. Demographics – Pooled Safety Population

-	AV7909 To Be Marketed N=3276 n (%)	BioThrax N=533 n (%)
Age (Years)	-	-
Mean (Std Dev)	39.0 (12.9)	38.7 (12.4)
Median (Min, Max)	38 (18, 65)	38 (18, 64)
Sex	-	-
Female	1895 (57.8)	293 (55.0)
Male	1381 (42.2)	240 (45.0)
Race	-	-
White	2553 (77.9)	416 (78.0)
Black/African American	561 (17.1)	88 (16.5)
Other/More than One Race	162 (4.9)	29 (5.4)
Ethnicity	-	-
Not Hispanic/Latino	2747 (83.9)	425 (79.7)
Hispanic/Latino	493 (15.0)	98 (18.4)
Not Reported	36 (1.1)	10 (1.9)

Source: Table 11.1.1.2a submitted to STN 125761/0.27.

Reviewer Comment:

- A total of 3151 AV7909 recipients from Study EBS.AVA.212 contributed to the integrated analysis, accounting for approximately 96% of the sample size of the to-be-marketed formulation. Therefore, it is expected that the ISS results would be similar to those presented for Study EBS.AVA.212 alone.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

There are no caveats to be noted for this analysis.

8.4 Safety Results

Table 20 presents the numbers and percentages of participants who reported any local or systemic reaction within 7 days of any AV7909 or BioThrax injection. Reactions reported after placebo administration in Study EBS.AVA.212 were excluded. The most commonly reported reactions after vaccination with AV7909 were tenderness (87.9%), pain (86.1%), and muscle ache (74.6%). Frequencies of local reactions were similar or higher among BioThrax recipients except for arm motion limitation, while frequencies of systemic reactions were generally higher among AV7909 recipients.

Table 20. Solicited Reactions within 7 Days of Any Dose – Pooled Safety Population

	AV7909 To Be Marketed n/N (%)	BioThrax n/N (%)
Injection Site Reaction	-	-
Arm Motion Limitation	2051/3230 (63.5)	271/527 (51.4)

	AV7909 To Be Marketed n/N (%)	BioThrax n/N (%)
Grade ≥ 3	53/3230 (1.6)	2/527 (0.4)
Axillary Adenopathy	0/17	NA
Grade ≥ 3	0/17	NA
Bruising	519/3213 (16.2)	184/527 (34.9)
Grade ≥ 3	9/3213 (0.3)	0/527
Edema	1/17 (5.9)	NA
Grade ≥ 3	0/17	NA
Induration	1175/3186 (36.9)	398/527 (75.5)
Grade ≥ 3	11/3186 (0.3)	6/527 (1.1)
Itching	686/3230 (21.2)	310/527 (58.8)
Grade ≥ 3	12/3230 (0.4)	4/527 (0.8)
Lump	13/44 (29.5)	NA
Grade ≥ 3	0/44	NA
Pain	2780/3230 (86.1)	463/527 (87.9)
Grade ≥ 3	68/3230 (2.1)	5/527 (0.9)
Erythema/Redness	572/3230 (17.7)	284/527 (53.9)
Grade ≥ 3	29/3230 (0.9)	10/527 (1.9)
Swelling	639/3230 (19.8)	292/527 (55.4)
Grade ≥ 3	13/3230 (0.4)	7/527 (1.3)
Tenderness	2840/3230 (87.9)	474/527 (89.9)
Grade ≥ 3	51/3230 (1.6)	4/527 (0.8)
Warmth	1623/3230 (50.2)	362/527 (68.7)
Grade ≥ 3	21/3230 (0.7)	1/527 (0.2)
Systemic Reaction	-	-
Tiredness	2125/3230 (65.8)	283/527 (53.7)
Grade ≥ 3	94/3230 (2.9)	9/527 (1.7)
Headache	1815/3230 (56.2)	251/527 (47.6)
Grade ≥ 3	104/3230 (3.2)	11/527 (2.1)
Muscle Ache	2409/3230 (74.6)	334/527 (63.4)
Grade ≥ 3	109/3230 (3.4)	10/527 (1.9)
Nausea	2/17 (11.8)	NA
Grade ≥ 3	0/17	NA
Fever	213/3236 (6.6)	9/527 (1.7)
Grade ≥ 3	23/3236 (0.7)	2/527 (0.4)

N = number of participants in the Safety Population who reported any e-diary data.

n = number of participants reporting the event.

NA = not applicable.

Source: Table 11.1.10.1b submitted to STN 125761/0.31.

The percentage of participants in each group who reported any AE after vaccination are shown in Table 21. As in Study EBS.AVA.212, a higher percentage of BioThrax recipients reported any AE, while a higher percentage of AV7909 recipients (1.9%) reported any SAE compared with BioThrax recipients (0.8%). A total of 6 deaths were reported, all of whom received AV7909 in Study EBS.AVA.212, with none assessed as related to the study vaccination by the investigator.

Table 21. Summary of Unsolicited AEs – Pooled Safety Population

	AV7909 To Be Marketed N=3276 n (%)	BioThrax N=533 n (%)
AEs	1294 (39.5)	251 (47.1)
Related	487 (14.9)	169 (31.7)
Grade ≥ 3 AEs	213 (6.5)	29 (5.4)
Related to any treatment	44 (1.3)	8 (1.5)
SAEs	62 (1.9)	4 (0.8)
Related to any treatment	1 (<0.1)	1 (0.2)
Deaths	6 (0.2)	0
Related	0	0
AESIs	15 (0.5)	2 (0.4)
Related	3 (0.1)	1 (0.2)
AEs leading to discontinuation of vaccination	75 (2.3)	13 (2.4)
AEs leading to study withdrawal	2 (0.1)	0

N = number of participants in the Safety Population.

n = number of participants reporting the event.

Source: Table 11.1.2.1a submitted to STN 125761/0.38.

8.5 Additional Safety Evaluations

No additional safety evaluations are considered in this review.

8.6 Safety Conclusions

I defer to the clinical reviewer on the overall safety conclusions.

9. ADDITIONAL STATISTICAL ISSUES

There are no additional statistical issues.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

In Study EBS.AVA.210, equivalence of ciprofloxacin steady-state PK parameters prior to vs. after AV7909 coadministration was met for both AUC_{0-12h} (GMR = 0.98; 90% CI: 0.89 to 1.07) and C_{max} (GMR = 0.97; 90% CI: 0.87 to 1.08). Equivalence of doxycycline steady-state PK parameters prior to vs. after AV7909 coadministration was met for AUC_{0-12h} (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). The Day 37 NF50 GMT in the AV7909/ciprofloxacin coadministration group was noninferior to that of the AV7909 single administration group (GMR = 1.13; 95% CI = 0.78 to 1.64). In the AV7909/doxycycline coadministration group, the GMR was 1.14 with 95% CI 0.81 to 1.60.

In Study EBS.AVA.212, lot consistency based on Day 64 NF50 GMTs was demonstrated. Among participants who received AV7909 in the PP Population, 66.3% (95% CI: 64.4% to 68.1%) achieved Day 64 NF50 ≥ 0.56 . In addition, AV7909 was noninferior to BioThrax in terms of the percentage of participants achieving Day 64 NF50 ≥ 0.29 (difference [AV7909 minus BioThrax] = 25.2%; 95% CI: 20.5% to 30.1%). Based on data from the NHP challenge Study 3655-100072763 and the immune responses observed among AV7909 recipients, the PVE of AV7909 was 96.8% (95% CI: 92.4% to 98.9%) on Day 29 and 82.9% (95% CI: 55.1% to 96.7%) on Day 64.

The most commonly reported reactions after vaccination with AV7909 were tenderness, pain, and muscle ache, with most being mild or moderate in severity. Compared with BioThrax, frequencies of local reactions after AV7909 vaccination were similar or lower, except for arm motion limitation, while frequencies of systemic reactions were generally higher. Numerically higher frequencies of SAEs and deaths were observed among AV7909 recipients in Study EBS.AVA.212 compared with BioThrax recipients. There were no notable differences in the percentages of participants reporting any AE leading to vaccination discontinuation, AE leading to study withdrawal, or AESI.

10.2 Conclusions and Recommendations

Based on data from Studies EBS.AVA.210 and EBS.AVA.212, two IM doses of AV7909 given two weeks apart elicits noninferior immune responses to three SC doses of BioThrax. Vaccination with AV7909 does not appear to meaningfully interfere with ciprofloxacin PK, but equivalence was not demonstrated with respect to doxycycline PK. In addition, data suggest no notable interference on the immune response to AV7909 after coadministration with ciprofloxacin or doxycycline.

I defer to the clinical reviewer on the overall safety conclusion.