OFFICE OF CLINICAL PHARMACOLOGY REVIEW

Reviewer: Xiaohui (Tracey) Wei, Ph.D.	Team Leader: Zhixia (Grace) Danielsen, Ph.D.

Consult No.: ICCR# 00861829 (CBER)	BLA No.: 125761	SN/SDN: N/A	DATE OF SUBMISSION: 8/2/2022

NAME OF DRUG/FORMULATION: **CYFENDUS (AV7909: Anthrax Vaccine Adsorbed, Adjuvanted with CpG 7909) Co-administration with Ciprofloxacin and Doxycycline**	ROUTE OF ADMINISTRATION: Intramuscular injection for AV7909 Oral for Ciprofloxacin and Doxycycline

INDICATION: **Post-exposure prophylaxis (PEP) of disease following suspected or confirmed exposure to *Bacillus anthracis* in persons 18-65 years of age**	DOSE (if known): Ciprofloxacin: 500 mg every 12 hours (q12h) per day Doxycycline: 100 mg q12h per day

SPONSOR: Emergent BioSolutions

TYPE OF SUBMISSION

☐ MEETING PACKAGE
    ☐ PIND   ☐ PreNDA
    ☐ EOP1   ☐ Type B
    ☐ EOP2A   ☐ Type C
    ☐ EOP2   ☐ Other

☐ NON-CLINICAL PK/ADME
☐ 30-DAY SAFETY SUBMISSION
☐ PROTOCOL/AMENDMENT
☐ PMR/PMC RELATED
☐ PHARMACOMETRICS
☐ PEDIATRIC RELATED/PSP

☐ INFORMATION AMENDMENT
☐ GENERAL CORRESPONDENCE
☐ ANNUAL REPORT
☒ CONSULT
☐ OTHER *(SPECIFY BELOW)*
    [   ]

REVIEW ACTION

☐ Submission acceptable from a Clinical Pharmacology perspective
☐ Comments to Sponsor via email/facsimile/meeting minutes dated:
☒ OTHER *(PLEASE SPECIFY)*: Provide responses to the questions requested by CBER

CBER review team requested DAI and DIDP's input on the Applicant's conclusions and proposed language regarding the vaccine-antimicrobial pharmacokinetic interaction for the co-administration of anthrax vaccine, AV7909 with ciprofloxacin or doxycycline in the package insert (USPI) for the adjuvanted anthrax vaccine, AV7909 (CYFENDUS). We reviewed the study report and responded to the questions from CBER consult request as noted at the end of this review.

BACKGROUND
AV7909 (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 the recommended antibacterial regimen. AV7909 is administered intramuscularly (IM) as a two-dose regimen, each containing 0.5 mL of AV7909, given two weeks apart on Days 1 and 15 for prevention of suspected or confirmed *B. anthracis* infection.

Study EBS.AVA.210 is a randomized, open-label, phase 2, multi-center drug-vaccine interaction study that examined whether co-administration of AV7909 with ciprofloxacin or doxycycline affects antibiotic PK or AV7909 immunogenicity in healthy adults 18-45 years of age. Potential effects of AV7909 vaccination on ciprofloxacin or doxycycline serum levels were investigated by evaluating changes in single-dose and steady-state PK profiles of ciprofloxacin or doxycycline before and after vaccination with a two-dose series of AV7909.

REQUEST FROM CBER
CBER review team sought DAI and DIDP's input on the Applicant's conclusions and proposed language regarding the vaccine-antimicrobial pharmacokinetic interaction for the co-administration of anthrax vaccine, AV7909 with ciprofloxacin or doxycycline in Sections 7.1 (DRUG INTERACTIONS) and 14.2 (CLINICAL STUDIES) of the package insert (USPI) for the adjuvanted anthrax vaccine, AV7909 (CYFENDUS). The scope of this clinical pharmacology consult includes an assessment of the Sponsor's drug-vaccine interaction study results and the proposed labeling language for AV7090.

DRUG-VACCINE INTERACTION RESULTS FROM STUDY EBS.AVA.210

Study title: A Phase 2 Drug-Vaccine Interaction Study to Examine Whether Co-administering AV7909 with Ciprofloxacin or Doxycycline Affects Antibiotic Pharmacokinetics or AV7909 Immunogenicity in Healthy Adults

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 2-dose schedule of AV7909 administered two weeks apart.

Primary Endpoints:
- Area under the curve from 0 to 12 hours (AUC_{0-12h}) and maximum concentration (C_{max}) at steady state for ciprofloxacin on Days 8 and 35;
- Steady state AUC_{0-12h} and C_{max} for doxycycline on Days 8 and 38.

Secondary Endpoints:
- AUC_{0-12h} and C_{max} following single dose for ciprofloxacin on Days 4 and 31 and for doxycycline on Days 2 and 32

Study Design:
Healthy males and females 18 to 45 years of age (N=210 planned participants) who met the entry criteria on Day 1 were randomized at a 1:1:1 ratio into one of the following three groups: Group 1: ciprofloxacin plus AV7909 (assigned to either 1A or 1B), Group 2: doxycycline plus AV7909 (assigned to either 2A or 2B), and Group 3: AV7909 alone as shown in Table 1.

Table 1. Study Groups

| IP Group	Treatment Group	Treatment	Planned Sample Size (N)	
1 Ciprofloxacin	1A	AV7909 + ciprofloxacin (with PK assessment)	40	70
	1B	AV7909 + ciprofloxacin (without PK assessment)	30	
2 Doxycycline	2A	AV7909 + doxycycline (with PK assessment)	40	70
	2B	AV7909 + doxycycline (without PK assessment)	30	
3 AV7909	3	AV7909 only		70
				210

Participants in Groups 1A and 2A received their first AV7909 vaccination after the 12-hour antibiotic PK sample (and after evening dose of the antibiotic) on Day 8, and their second AV7909 vaccination on Day 23.

Ciprofloxacin (500 mg per os [po] every 12 [q12] hours) was administered to participants in Group 1 on Days 4 through 9, Days 22 through 24, and Days 31 through 37. Ciprofloxacin PK sampling in Group 1A were conducted on Days 4, 8, 31, and 35. Ciprofloxacin pre-dose or trough values were measured prior to the morning doses of ciprofloxacin on Days 4, 5, 6, 7, 8, and again on Days 31, 32, 33, 34, and 35. On the days with serial PK sampling, blood samples for measurement of ciprofloxacin 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 post-dose.

Doxycycline (100 mg by po q12 hours) was administered to participants in Group 2 on Days 2 through 9, Days 22 through 24, and Days 32 through 38. Doxycycline PK sampling in Group 2A were conducted on Days 2, 8, 32, and 38. Doxycycline pre-dose or trough values were measured prior to the morning doses of doxycycline on Days 2, 3, 4, 5, 6, 7, 8, and again on Days 32, 33, 34, 35, 36, 37, and 38. On the days with PK sampling, blood samples for measurement of doxycycline 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 post-dose.

The overall study schema is displayed in Figure 1.

Figure 1. Figure 1 Overall Study Schema
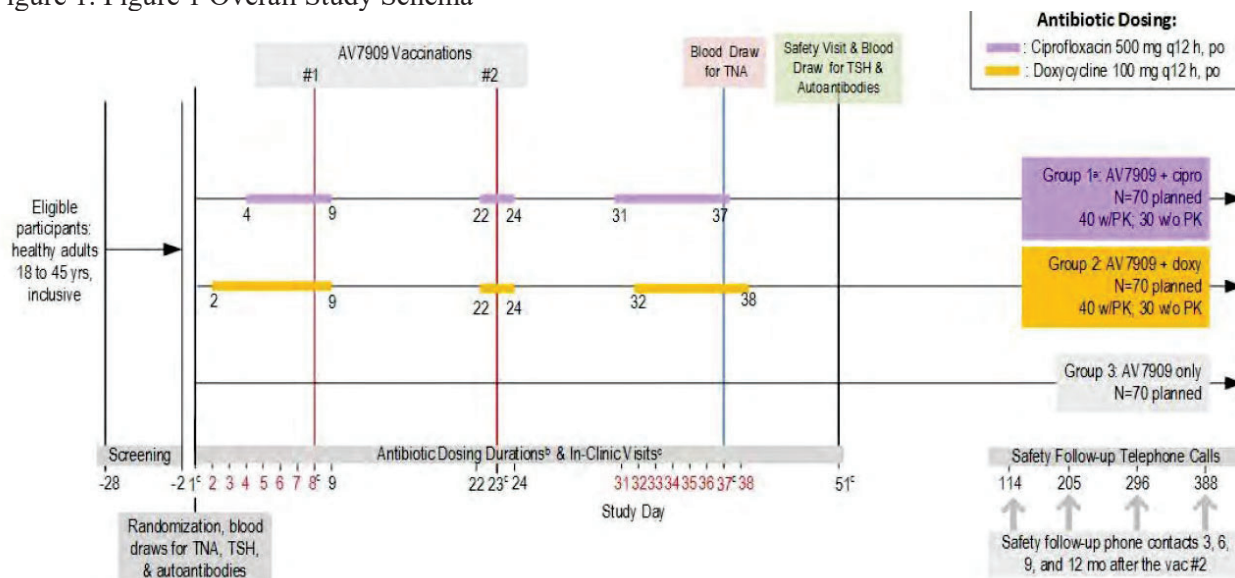
The Sponsor stated that antibiotic administration was intermittent rather than continuous to reduce antibiotic exposure, thereby presumably reducing the risks of adverse effects from these antibiotics in the healthy participants. The AV7909 only group (Group 3) served as the control group. Group 3 was designed to be used in a non-inferiority comparison of AV7909 vaccination versus AV7909 + antibiotic (Groups 1 or 2) to evaluate whether the combined exposure interfered with the immune response to AV7909.

Reviewer's comments: Based on the input from CBER reviewer, the maximum effect of vaccine on antibiotics would be 2 weeks post-vaccination. Therefore, post-vaccine PK assessment of ciprofloxacin and doxycycline was conducted following dosing of ciprofloxacin and doxycycline at around 15 days after the second dose of AV7909 vaccine when the peak vaccine immunogenicity effect is expected.

Pharmacokinetics Results
Ciprofloxacin PK Results and Analysis
The Sponsor claimed that visual inspection (Figure 2) and statistical assessment of trough concentrations versus treatment day indicated that steady-state was achieved prior to the steady-state PK assessment days on Day 8 and Day 35. Therefore, the Day 8 and Day 35 PK parameters were calculated under steady-state conditions. The arithmetic mean ciprofloxacin trough concentrations were lower post-AV7909 vaccination compared to pre-vaccination trough concentrations, but with overlapping SDs.

Figure 2. Mean (±SD) Trough Concentration-time Profiles by Day for Ciprofloxacin (Pharmacokinetic Population)
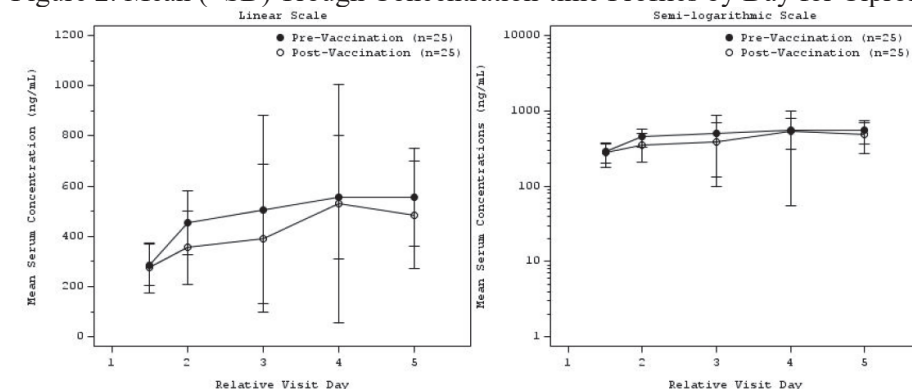
Pre- and post-vaccine ciprofloxacin exposures (AUC_{0-12h}, C_{max}, C_{trough}) following single or repeated dosing are summarized in Table 4. The results of the statistical comparison of the ciprofloxacin exposure parameters (AUC_{0-12h} and C_{max}) for the primary and secondary PK endpoint are presented in Table 2. For the primary PK steady-state ciprofloxacin PK endpoint, following administration of ciprofloxacin pre- (Day 8) and post-AV7909 vaccination (Day 35), the 90% CIs of the mean ratios of the steady-state AUC_{0-12h}, C_{max} were fully contained within the pre-defined equivalence criteria of [0.80, 1.25], therefore meeting the primary ciprofloxacin PK (steady-state) objective. For the secondary endpoint, following a single dose administration of ciprofloxacin on Day 4 and Day 31, the lower bounds of the 90% CIs of the mean ratios of AUC_{0-12h} [90% CI: 0.7851, 1.0966] and C_{max} [90% CI: 0.7895, 1.1332] were below the predefined equivalence criteria of [0.80, 1.25], hence,

the secondary PK objective for single dose ciprofloxacin was not met.

Table 2. Equivalence Test of Primary and Secondary Pharmacokinetic Analysis for Ciprofloxacin

	PK Parameter (unit)	Comparison (Post-vac. vs Pre-vac)	Number of Subjects Assigned for PK Assessment	PK Population	Number of Non-missing Pairs	Geometric Mean of Ratios (Post-vac./Pre-vac)	90% CI for Geometric Mean of Ratios
Primary PK endpoint	AUC_{0-12h} (h*ng/mL)	Day 35 vs Day 8	41	25	25	0.9764	(0.8895, 1.0718)
	C_{max} (ng/mL)	Day 35 vs Day 8	41	25	25	0.9706	(0.8693, 1.0838)
Secondary PK endpoint	AUC_{0-12h} (h*ng/mL)	Day 31 vs Day 4	41	25	24	0.9278	(0.7851, 1.0966)
	C_{max} (ng/mL)	Day 31 vs Day 4	41	25	24	0.9459	(0.7895, 1.1332)

Abbreviations: CI = confidence interval; PK = pharmacokinetic; Post-vac. = post-vaccination; Pre-vac = pre-vaccination.

Doxycycline PK Results and Analysis
The Sponsor claimed that visual inspection (Figure 3) and statistical assessment of trough concentrations versus treatment day indicated that steady-state was achieved pre-vaccination, but not post-vaccination. The arithmetic mean doxycycline trough concentrations were generally lower post-vaccination compared to pre-vaccination, but with overlapping SDs.

Figure 3. Mean (±SD) Trough Concentration-time Profiles by Day for Doxycycline
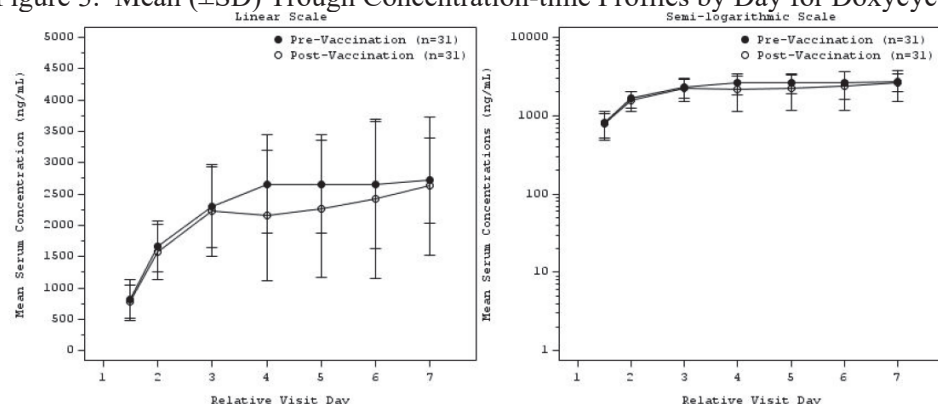
Pre- and post-vaccine doxycycline exposures (AUC_{0-12h}, C_{max}, C_{trough}) following single or repeated dosing are summarized in Table 5. The results of the statistical comparison of the doxycycline exposure parameters (AUC_{0-12h}, C_{max}) for the primary and secondary PK endpoint are presented in Table 3. For the primary PK steady-state doxycycline endpoint, following administration of doxycycline pre-(Day 8) and post-AV7909 vaccination (Day 38), the 90% CI of the mean ratio of steady-state AUC_{0-12h} [90% CI: 0.8187, 1.0278] was fully contained within the predefined equivalence criteria of [0.80, 1.25] with an approximately 8% lower geometric mean of the ratios. However, the lower bound of the 90% CI of the mean ratio of steady-state C_{max} [90% CI: 0.7841, 1.0271] was not within the predefined equivalence limits, therefore not meeting the primary PK doxycycline objective. The secondary doxycycline PK endpoint was evaluated and reported for information only. The 90% CI of the geometric mean ratio for single-dose C_{max} [90% CI: 0.8224, 1.2361] was fully contained within the predefined equivalence criteria of [0.80 to 1.25], while the upper bound of the 90% CI of the geometric mean ratio for single-dose AUC_{0-12h} [90% CI: 0.8636, 1.2829] was above the predefined equivalence limits.

Table 3. Equivalence Test of Primary and Secondary Pharmacokinetic Analysis for Doxycycline

	PK Parameter (unit)	Comparison (Post-vac. vs Pre-vac)	Number of Subjects Assigned for PK Assessment	PK Population	Number of Non-missing Pairs	Geometric Mean of Ratios (Post-vac./Pre-vac)	90% CI for Geometric Mean of Ratios
Primary PK endpoint	AUC_{0-12h} (h*ng/mL)	Day 38 vs Day 8	42	31	30	0.9173	(0.8187, 1.0278)
	C_{max} (ng/mL)	Day 38 vs Day 8	42	31	31	0.8974	(0.7841, 1.0271)
Secondary PK endpoint	AUC_{0-12h} (h*ng/mL)	Day 32 vs Day 2	42	31	26	1.0525	(0.8636, 1.2829)
	C_{max} (ng/mL)	Day 32 vs Day 2	42	31	26	1.0082	(0.8224, 1.2361)

Abbreviations: CI = confidence interval; PK = pharmacokinetic; Post-vac. = post-vaccination; Pre-vac = pre-vaccination.

THE APPLICANT'S PROPOSED LANGUAGE IN LABELING OF AV7909

Based on the PK findings of Study EBS.AVA.210, the Applicant proposes the following language in Sub-Section 7.1 (b) (4) under Section 7.0 DRUG INTERACTIONS of the USPI:

(b) (4)

The Applicant also proposes additional language pertaining to the PK findings from EBS.AVA.210 under Section 14.2 'Co-Administration with Ciprofloxacin and Doxycycline':

"A randomized, open-label, multicenter study (Study 3; NCT04067011) was conducted in healthy males and females, age 18 to 45 years, to investigate the potential interactions of concomitant IM administration of CYFENDUS vaccine with oral administration of ciprofloxacin or doxycycline. The potential effect of CYFENDUS vaccination on ciprofloxacin or doxycycline serum levels was assessed by evaluating steady-state PK profiles of ciprofloxacin or doxycycline before and after vaccination with a two-dose series of CYFENDUS vaccine.

Co-administration of 0.5 mL of CYFENDUS vaccine intramuscularly with oral ciprofloxacin or doxycycline in human participants did not alter the relevant PK parameters of ciprofloxacin and doxycycline, or the immunogenicity of CYFENDUS vaccine as measured by the TNA assay."

CLINICAL PHARMACOLOGY ASSESSMENTS AND RESPONSES

We evaluated the PK results from Study EBS.AVA.210 as well as PK data reported from literature and from ciprofloxacin label (CIPRO®), doxycycline label (DORYX®) that include the indication of inhalational anthrax post-exposure prophylaxis (PEP).

Table 4 summarizes the pre- and post-vaccine ciprofloxacin mean exposures (AUC_{0-12h}, C_{max}, C_{trough}) following single 500 mg oral dose or repeated oral administration at 500 mg q12h, as reported from Study EBS.AVA.210. Ciprofloxacin exposures reported from CIPRO® label are included for comparison. As shown in Table 4, ciprofloxacin pre- or post-vaccine exposures (AUC_{0-12h}, C_{max}, C_{trough}) determined from Study EBS.AVA.210 are similar to the exposures reported from CIPRO® label.

Table 4 also includes ciprofloxacin concentrations and MIC values determined from a rhesus monkey model challenged with inhaled *B. anthracis*. The ciprofloxacin concentrations and MIC values are reported under Section 14.2 "Inhalational Anthrax in Adults and Pediatrics" in CIPRO® label. In this section, it states that from a placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~5.5 x 105 spores (range 5–30 LD50)) of *B. anthracis*, mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post- exposure was significantly lower (1/9), compared to the placebo group (9/10) [p= 0.001]. Therefore, the ciprofloxacin concentrations determined from this rhesus monkey anthrax study can be viewed as the efficacious concentrations for the post-exposure prophylaxis of anthrax. As shown in Table 4, ciprofloxacin pre- or post-vaccine average C_{max} and C_{trough} levels reported from Study EBS.AVA.210 exceed the respective C_{max} and C_{trough} levels that are associated with improved survival in the rhesus monkey's anthrax model.

Results from the statistical analyses conducted by the Applicant showed that, following a single dose administration of ciprofloxacin on pre- (Day 4) and post-AV7909 vaccination (Day 31), the lower bounds of the 90% CIs of the mean ratios of

AUC_{0-12h} [90% CI: 0.7851, 1.0966] and C_{max} [90% CI: 0.7895, 1.1332] were slightly below the predefined equivalence criteria of [0.80, 1.25]. However, the pre- and post- vaccine ciprofloxacin exposures (AUC_{0-12h}, C_{max}) following single dose are similar to the exposures in human subjects as reported from CIPRO® label and exceed the efficacious exposures and MIC values determined from rhesus monkey's anthrax model. Therefore, we consider that the findings of single-dose PK differences for ciprofloxacin pre- versus post-AV7909 vaccine are not clinically relevant in a PEP setting where ciprofloxacin would be administered with AV7909 vaccine.

Table 4. Ciprofloxacin Exposures (Geometric CVs [%]) in Humans and Rhesus monkeys and MIC Value from Rhesus Monkeys

Source	Dosing status	AUC_{0-12h} (µg.h/mL)	C_{max} (µg/mL)	C_{trough} (µg/mL)	MIC (µg/mL)
Human, Study EBS.AVA.210	Single dose, pre-vaccine	9.90 (38.2)	2.48 (49.3)	0.29 (28.8)	
	Single dose, post-vaccine	9.17 (44.8)	2.38 (46.4)	0.27 (36)	
	Steady state, pre-vaccine	13.2 (34.1)	2.92 (38.4)	0.56 (35)	
	Steady state, post-vaccine	12.9 (30.5)	2.84 (35.3)	0.49 (43.9)	
Human, CIPRO® label Section 12.3 Pharmacokinetics	Single dose	11.6[1]	2.4		
	Steady state	13.7[2]	2.97		
Human, CIPRO® label Section 14.2 Inhalational Anthrax in Adults and Pediatrics	Steady state		2.97	0.2	
Rhesus monkey model with inhaled *B. anthracis*, CIPRO® label Section 14.2	Steady state		0.98 to 1.69	0.12 to 0.19	0.08

Ciprofloxacin doses in human subjects from Study EBS.AVA.210 and CIPRO® label: single dose: 500 mg orally; multiple doses: 500 mg q12h orally
[1]: Reported as AUC in the CIPRO® label; [2]: Calculated as CIPRO® label reported AUC_{0-24h} /2

Table 5 summarizes doxycycline pre- and post-vaccine exposures (AUC_{0-12h}, C_{max}, C_{trough}) following single 100 mg oral dose or repeated oral administration at 100 mg q12h as reported from Study EBS.AVA.210. Doxycycline exposures reported from literature and DOXY® label are included for comparison. Doxycycline exposures in humans (e.g., AUC, C_{max}) are variable based on the limited data reported in literature 1 (see References below). As shown in Table 5, doxycycline pre- or post-vaccine exposures (AUC_{0-12h}, C_{max}) determined from Study EBS.AVA.210 are generally similar to the exposures reported from literature and DOXY® label.

Literature 2 and 3 report doxycycline concentrations and MIC values from a rhesus monkey model challenged with inhaled *B. anthracis.* In the placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 8 LD_{50} (~4.0 x 10^5 spores) *B. anthracis*, mortality due to anthrax for animals that received a 30-day regimen of oral doxycycline beginning 24 hours post- exposure was significantly lower (1/10), compared to the placebo group (9/10) [p= 0.001]. Therefore, the doxycycline concentrations determined from this rhesus monkey anthrax study can be viewed as the efficacious concentrations for the post-exposure prophylaxis of anthrax. Doxycycline pre- or post-vaccine average C_{max} and C_{trough} levels reported from Study EBS.AVA.210 exceed the respective C_{max} and C_{trough} levels that are associated with the improved survival in the rhesus monkey's anthrax model.

Results from the statistical analyses conducted by the Applicant showed that, the geometric mean values of steady-state post-vaccine AUC_{0-12h} is approximately 8% lower than the pre-vaccine value; the lower bound of the 90% CI of the mean ratio of steady-state C_{max} [90% CI: 0.7841, 1.0271] was not within the predefined equivalence limits. However, the post-vaccine C_{max} and C_{trough} levels were found exceeding the efficacious concentrations and MIC values determined from rhesus monkey's anthrax model. In addition, even though the upper bound of the 90% CI of the geometric mean ratio for single-dose AUC_{0-12h} [90% CI: 0.8636, 1.2829] was above the predefined equivalence limits, doxycycline exposures (AUC_{0-12h}, C_{max}) determined from Study EBS.AVA.210 are similar to the exposures reported in the DOXY® label and literature. Hence, we consider that the findings of steady-state and single-dose PK differences for doxycycline pre- versus post-AV7909 vaccine

are not clinically relevant in a PEP setting where doxycycline would be administered with AV7909 vaccine.

Table 5. Doxycycline Exposures (Geometric CVs [%]) in Humans and Rhesus Monkeys and MIC Value from Rhesus Monkeys

Source	Dosing status	AUC_{0-12h} (µg.h/mL)	C_{max} (µg/mL)	C_{trough} (µg/mL)	MIC (µg/mL)
Human, Study EBS.AVA.210	Single dose, pre-vaccine	11.2 (48.6)	1.56 (55.2)	0.81 (29.5)	
	Single dose, post-vaccine	11.6 (32.8)	1.55 (30.5)	0.79 (34.1)	
	Steady state, pre-vaccine	36.9 (22.1)	4.2 (21.7)	2.72 (25)	
	Steady state, post-vaccine	34 (40.8)	3.78 (48.9)	2.63 (42.3)	
Human, DORXY® label, Section 12.3	Single dose		2.3[1]		
	Multiple doses		3.2[1]		
Human, Literature 1	Single dose	37 to 40[2]	1.7		
	Multiple doses	13 ± 5[3]	2.0 ± 1.0[3]		
Rhesus monkey model with inhaled *B. anthracis*, Literature 2, 3	Steady state		0.81 to 1.96	0.20 to 0.36	0.02

Doxycycline doses in human subjects from Study EBS.AVA.210 and Literature 1: single dose: 100 mg orally; multiple doses: 100 mg q12h orally
[1]: Calculated as $C_{max}/2$ based on C_{max} values at 200 mg reported in DOXY® label; [2]: Reported as AUC in Literature 1; [3]: Mean ± SD

References:
Literature 1: Agwh KN et al. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. Journal of Antimicrobial Chemotherapy (2006) 58, 256–265
Literature 2: Kelly DJ, et al. Serum concentrations of penicillin, doxycycline, and ciprofloxacin during prolonged therapy in rhesus monkeys. J Infect Dis 1992; 166:1184-7.
Literature 3: Friedlander AM, et al. Postexposure prophylaxis against experimental inhalational anthrax. J Infect Dis 1993; 167:1239-42.

Below are our responses to the questions from CBER:

1. AV7909 antimicrobial interaction studies conducted under the PK interaction study EBS.AVA.210 showed that IM administration of a 2-dose series of AV7909 resulted in slightly lower doxycycline steady state levels (approximately 8-10% lower) and slightly lower single dose ciprofloxacin levels.
    a. Do you consider the steady-state and single-dose PK findings for doxycycline to be clinically relevant (meaningful) in a PEP setting where doxycycline would be administered with AV7909 vaccine? What information do you consider relevant for practitioners and important to include in the USPI for AV7909?

        Clinical Pharmacology Response: Based on the DOXY ® label and literature reported doxycycline exposures in humans and the efficacious exposures determined from the rhesus monkey's anthrax model, we consider that findings of the steady-state and single-dose PK differences for doxycycline post- versus pre-vaccine are not clinically relevant in a PEP setting where doxycycline would be administered with AV7909 vaccine. We recommend USPI language for Sections 7.1 and 14.2 be revised according to our responses under Question 2.

    b. Do you consider the single-dose PK finding for ciprofloxacin to be clinically relevant (meaningful) in a PEP setting where ciprofloxacin would be administered with AV7909 vaccine? What information do you consider relevant for practitioners and important to include in the USPI for AV7909?

        Clinical Pharmacology Response: Based on the CIPRO® label reported ciprofloxacin exposures in humans and the efficacious exposures determined from the rhesus monkey's anthrax model, we consider that the findings of single-dose PK differences for ciprofloxacin post- versus pre-vaccine are not clinically relevant

in a PEP setting where ciprofloxacin would be administered with AV7909 vaccine. We recommend USPI language for Sections 7.1 and 14.2 be revised according to our responses under Question 2.

2. Is the proposed UPSI language for Sections 7.1 and 14.2 (as provided above) for AV7909 supported by the PK findings of study EBS.AVA.210 pertaining to effects of AV7909 administration on the PK of ciprofloxacin and doxycycline? If not, how should the USPI language be revised for Section 7.1 and/or Section 14.2?

   Clinical Pharmacology Response*: To avoid redundancy with Sub-Section 14.2, we suggest making the following revisions in Sub-Section 7.1* **(b) (4)** *under Section 7.0 DRUG INTERACTIONS of the USPI:*

   (b) (4)

   We defer to CBER to include appropriate language for describing the effect of ciprofloxacin and doxycycline on the immunogenicity of CYFENDUS vaccine under Sub-Section 7.1.

   We suggest making the following revisions as shown bolded in Sub-Section 14.2 'Co-Administration with Ciprofloxacin and Doxycycline' of the USPI:

   "A randomized, open-label, multicenter study (Study 3; NCT04067011) was conducted in healthy males and females, age 18 to 45 years, to investigate the potential interactions of concomitant IM administration of CYFENDUS vaccine with oral administration of ciprofloxacin or doxycycline. The potential effect of CYFENDUS vaccination on ciprofloxacin or doxycycline serum levels was assessed by evaluating steady-state PK profiles of ciprofloxacin or doxycycline before and after vaccination with a two-dose series of CYFENDUS vaccine.

   Co-administration of 0.5 mL of CYFENDUS vaccine intramuscularly with oral ciprofloxacin or doxycycline in human participants **did not have a clinically relevant impact on** the pharmacokinetics of ciprofloxacin and doxycycline, or the immunogenicity of CYFENDUS vaccine as measured by the TNA assay."

   We defer to CBER to confirm or modify the language for describing the effect of ciprofloxacin and doxycycline on the immunogenicity of CYFENDUS vaccine under Sub-Section 14.2.

3. Do you have any other recommendations or comments outside of our specific questions?

   Clinical Pharmacology Response*: No, we do not have additional comments or recommendations. However, our proposed USPI languages in Sub-Sections 7.1 and 14.2 are for recommendations only. We defer to CBER on the final labeling language regarding the interaction between CYFENDUS vaccine and ciprofloxacin/doxycycline.*

SIGNATURE OF REVIEWER: _Xiaohui Wei -S_ Digitally signed by Xiaohui Wei S Date: 2022 09 01 17:31 42 04'00'   Date _9/1/2022_____

SIGNATURE OF TEAM LEADER: _Zhixia Y. Danielsen -S_ Digitally s gned by Zhixia Y Danielsen S Date: 2022 09 01 17:26:38 04'00'   Date __9/1/2022_____

Taruna Khurana -S
Digitally signed by Taruna Khurana -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Taruna Khurana -S, 0.9.2342.19200300.100.1.1=1300411163
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