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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

Clinical Protocol EBS.AVA.210

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SPONSOR'S SIGNATURE PAGE

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Protocol Number: EBS.AVA.210

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[redacted] Date

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[redacted] Date

[redacted] Date

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INVESTIGATOR'S AGREEMENT

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that the study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. State and federal regulations and International Council for Harmonisation (ICH) guidelines.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the product and the conduct of the study.

I agree that all information pertaining to the study, including protocols, electronic case report forms (eCRFs), and verbal and written consent information will be kept strictly confidential. Distribution of such information or information on the conduct, progress, or results of the study will be restricted to the clinical personnel involved with the conduct of the study, members of the Institutional Review Board/Independent Ethics Committee (IRB/IEC), and/or regulatory authorities.

I understand that Emergent Product Development Gaithersburg Inc. (Emergent), its representatives, representatives from the Biomedical Advanced Research and Development Authority (BARDA) and regulatory agencies shall have access to any documents relevant to the study, including documents that demonstrate protocol and regulatory compliance.

_____

Printed Name of Principal Investigator

_____

Signature of Principal Investigator

_____

Date

[redacted]

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LIST OF ABBREVIATIONS/SPECIALIST TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations/Specialist Terms

Abbreviation/Specialist Term	Definition
ACC	American College of Cardiologists
ACIP	Advisory Committee on Immunization Practices
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse event
AESI	Adverse event of special interest
AHA	American Heart Association
aIG	Animal derived immune globulin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
$AUC_{0\text{-}12h}$	Area under the concentration-time curve from t=0 to 12 hours
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from t=0 to infinity
$AUC_{0\text{-}t}$	Area under the concentration-time curve from t=0 to last measurable concentration
AUMC	Area under the first moment curve
AVA	Anthrax vaccine adsorbed, BioThrax.
AV7909	AVA plus CPG 7909, an investigational product
B. anthracis	*Bacillus anthracis*
BARDA	Biomedical Advanced Research and Development Authority
BioThrax	BioThrax® (Anthrax Vaccine Adsorbed)
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood cell count
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention

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Abbreviation/Specialist Term	Definition
CFR	Code of Federal Regulations
CI	Confidence interval
Cipro	Ciprofloxacin
C_{max}	Maximum concentration
CNS	Central nervous system
CPG 7909	A synthetic oligonucleotide used as an adjuvant
CRO	Contract research organization
C_t	Last measurable concentration
CV	Coefficient of variation
d	Day(s)
dL	Deciliter
DM	Diabetes mellitus
DMP	Data Management Plan
Doxy	Doxycycline
DRESS	Drug reaction with eosinophilia and systemic symptoms
dsDNA	Double-stranded deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
e-diary	Electronic diary
[redacted]	[redacted]
ER	Emergency room
EWV	Early withdrawal visit
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practices
GERD	Gastroesophageal reflux disease
GLP	Good Laboratory Practices
GMC	Geometric mean concentration

[redacted]

Abbreviation/Specialist Term	Definition
GMT	Geometric mean titer
GUP	General use prophylaxis
HBsAg	Hepatitis B virus surface antigen
HCVAb	Hepatitis C virus antibody
hhIG	Human hyperimmune globulins
h/hr	Hour(s)
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HIVAb	Antibody to human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IGIM	Human immunoglobulins for intravenous injection
IGIV	Human immunoglobulins for intravenous injection
IGSC	Human immunoglobulins for subcutaneous injection
IH	Intracranial hypertension
IM	Intramuscular
IND	Investigational New Drug (application)
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
IXRS	Interactive voice/web response system
kDa	Kilodalton
K_{el}	Elimination rate constant
LD_{50}	Dose at which 50% mortality is observed
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities

[redacted]

Abbreviation/Specialist Term	Definition
mEq	MilliEquivalents
mg	Milligram
min	Minute(s)
mIU/mL	Milli-international units per milliliter
MM	Medical Monitor
MRT	Mean residence time
NB	Note well (nota bene)
NF_{50}	50% neutralization factor
NHP	Nonhuman primate
NOSTASOT	No statistical significance of trend
NSAID	Non-steroidal anti-inflammatory drug
ODN	Oligodeoxynucleotide
OHRP	Office of Human Research Protection
PA	Protective antigen
PE	Physical examination
PEP	Post-exposure prophylaxis
PI	Principal Investigator
PK	Pharmacokinetic(s)
po	Per os (orally)
PRBC	Packed red blood cells
PT	Preferred term (MedDRA)
PV	Pharmacovigilance
q 12 hr	Every 12 hours
QA	Quality Assurance
QC	Quality Control
RBC/hpf	Red blood cells/high powered field
RF	Rheumatoid factor
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous

[redacted]

Abbreviation/Specialist Term	Definition
SOC	System Organ Class level of MedDRA
SOP	Standard operating procedure
Subject ID	A unique identifier assigned to each study participant
SUSAR	Suspected unexpected serious adverse reaction
SV	Study visit
$t_{1/2}$	Elimination half-life
TBD	To be determined
TEAE	Treatment emergent adverse event
t_{max}	Time to maximum concentration
TNA	Toxin neutralizing antibody
TOST	Two one-sided t-tests
TSH	Thyroid stimulating hormone
UAT	User acceptability testing
ULN	Upper limit of normal
UPT	Urine pregnancy test
USP	United States Pharmacopeia
USV	Unscheduled Visit
UVA/UVB	Ultraviolet radiation A/B
Vac	Vaccination
WBC	White blood cell count
WHO	World Health Organization
WOCBP	Woman of childbearing potential

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1. SYNOPSIS

Name of Sponsor/Company: [redacted]	
Name of Investigational Product: AV7909	
Name of Active Ingredient: AVA drug substance and CPG 7909 as adjuvant	
Name of Co-Administered Products: Ciprofloxacin hydrochloride; Doxycycline hyclate	
Title of Study: 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	
Short Title: PEP Antibiotic-AV7909 Interaction Study	
Study center(s): Up to five sites in the United States (US)	
Studied period (months): Individual participants enrollment in the study from the screening visit to the last visit and all safety follow-up calls will be approximately 14.5 months. Screening will be from Day -28 to Day -2 followed by either 19 (Group 2A), 17 (Group 1A) or 6 (Groups 1B, 2B and 3) in-clinic visits occurring over six weeks. Safety follow-up phone calls will be conducted 3, 6, 9 and 12 months after the last vaccination. Overall study duration from the first participant first visit to last participant last visit is anticipated to be approximately 18 months.	**Phase of Development:** Phase 2
Objectives: **Primary:** • 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:** • 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.	

[redacted]

Study Design:

This is a randomized, open-label, phase 2, multicenter trial to investigate the potential interactions of AV7909 and ciprofloxacin or doxycycline when administered concomitantly. Healthy males and females between 18 and 45 years of age, inclusive, will read, sign and date an informed consent form and then be screened for eligibility for participation in the study. Participants (N=210) meeting the entry criteria on Day 1 will be randomized 1:1:1 into one of three investigational product (IP) groups as shown in the table below.

IP Group	Treatment Group	Treatment	Sample Size (N)	
1 Cipro	1A	AV7909 + ciprofloxacin (with PK assessment)	≈40	≈70
	1B	AV7909 + ciprofloxacin (without PK assessment)	30	
2 Doxy	2A	AV7909 + doxycycline (with PK assessment)	≈40	≈70
	2B	AV7909 + doxycycline (without PK assessment)	30	
3 AV7909	3	AV7909 only	70	
		TOTAL	≈210	

Approximately the first 40 participants who are randomized for either IP Groups 1 and 2, ie, the first 80 participants randomized across all sites to either antibiotic group, will be assigned to Treatment Groups 1A or 2A while those randomized into IP Groups 1 and 2 thereafter will be assigned to Treatment Groups 1B or 2B. Randomization will be stratified by site. A representative racial distribution will be sought among recruited participants and sites will be asked to recruit populations that are gender- and age-balanced (ie, between 40-60% male with 40-60% of participants in the two age ranges of 18 to 30 years of age and 31 to 45 years of age).

Figure 1 displays the overall design used for this study.

Ciprofloxacin (500 mg by mouth [per os] every 12 hours [po q 12 hr]) will be administered to Group 1 on Days 4-9, Days 22-24 and Days 31-37, and doxycycline (100 mg by mouth [per os] every 12 hours [po q 12 hr]) will be administered to Group 2 on Days 2-9, Days 22-24, and Days 32-38. Antibiotics will be administered in three courses that will be used both by site staff for in-clinic visits and by participants when they are at home. The exact format of the courses in terms of number of tablets and when participants will receive each course will be described in the Pharmacy Manual.

The 40 participants in Group 1A will self-administer approximately half (14/31) of the ciprofloxacin doses; the remainder will be administered by site staff during clinic visits. The 30 participants in Group 1B, with far fewer clinic visits than Group 1A due to the lack of PK sampling, will self-administer more than 90% (29/31) of ciprofloxacin doses.

[redacted]

For the doxycycline groups, the distributions of self-administered doses are similar to those planned for the two ciprofloxacin groups with Group 2A self-administering 15/35 doses and Group 2B self-administering 33/35 doses.

An event schematic for this study is provided in Figure 2.

Ciprofloxacin PK sessions in Group 1A will be conducted on Days 4, 8, 31 and 35. Ciprofloxacin pre-dose or trough values will be measured prior to the morning doses of ciprofloxacin on Days 4, 5, 6, 7 and 8 and again on Days 31, 32, 33, 34 and 35. On the days with PK sessions, blood samples for measurement of ciprofloxacin concentrations will be 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 (± 5 min through hr 4, then ± 15 min thereafter). The Schedules of Events for Group 1A and Group 1B are provided in Table 5 and Table 6, respectively.

Doxycycline PK sessions in Group 2A will be conducted on Days 2, 8, 32 and 38. Doxycycline pre-dose or trough values will be measured prior to the morning doses of doxycycline on Days 2, 3, 4, 5, 6, 7 and 8 and again on Days 32, 33, 34, 35, 36, 37 and 38. On the days with PK sessions, blood samples for measurement of doxycycline concentrations will be 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 (± 5 min through hr 4, then ± 15 min thereafter). The Schedules of Events for Group 2A and Group 2B are provided in Table 7 and Table 8, respectively.

All participants, including the 70 participants in Group 3, will receive AV7909 IM in the deltoid muscle of alternate arms on Days 8 and 23. For Groups 1A and 2A, the first vaccination will occur following completion of the PK sessions and after administration of the evening antibiotic (ciprofloxacin or doxycycline) dose. The Schedule of Events for Group 3 is provided in Table 9.

Blood draws for TNA assessments will be performed for all participants at randomization (Day 1) and on Day 37 (two weeks following the second and final vaccination).

Safety in all groups will be assessed up to Day 51 (or the early withdrawal visit [EWV]) by physical examinations, vital signs, clinical laboratories (hematology, serum chemistry, and urinalysis), monitoring of adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESIs; ie, of autoimmune etiology; see Table 14), concomitant medications, and injection site and systemic reactions as reported in participant electronic diaries (e-diaries). The severity of AEs, laboratory test results for select analytes, and vital sign results will be assessed based on the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*. Reactogenicity (solicited systemic and local injection site reactions) will be assessed daily by the participants using e-diaries for at least seven days after each vaccination. If local injection site or systemic reactions continue beyond seven days (d), participants will be prompted to continue e-diary entries until resolved for at least two consecutive days. Participants in Groups 1 and 2 will also use the e-diary to record their self-administration of antibiotics. Site staff will review e-diary entries on a routine basis and will review the e-diary record with each

[redacted]

participant at each study visit. Safety follow-up phone contacts to collect information on AEs, SAEs and AESIs will occur at 3 months (Day 114 ± 14 d), 6 months (Day 205 ± 14 d), 9 months (Day 296 ± 14 d) and 12 months (Day 388 ± 14 d) after the last scheduled vaccination.

Blood samples will be taken at randomization (Day 1) and Day 51 (or the EWV) to test (if medically indicated as per principal investigator's discretion based on a report of potential AESI) for thyroid stimulating hormone (TSH) levels, antinuclear antibodies (ANA), rheumatoid factor (RF) and anti-double stranded deoxyribonucleic acid (dsDNA) antibodies. Samples may also be collected at unscheduled visits following the safety follow-up phone contact(s) to investigate potential AESI reports.

Independent safety oversight will be provided by a Data Safety Monitoring Board (DSMB), which will be notified of significant AEs [eg, SAEs, severe AEs recorded on an electronic case report form (eCRF), potential AESIs of autoimmune etiology, or any other events the medical monitor deems medically relevant] as determined by the medical monitor on an ongoing basis. The DSMB will comprise at least three voting members, to include one expert in immunology to specifically support the evaluation of potential AESIs for autoimmune etiology, if pre-existing or new onset, and relationship to the study product. The DSMB will make recommendations regarding the safety of continuing enrollment and dosing. Study enrollment and dosing may be interrupted at the request of the DSMB Chair if it is believed that an AE represents a significant safety concern requiring suspension of dosing pending full DSMB evaluation. The operations of the DSMB will be detailed in a DSMB Charter which will be finalized prior to screening the first participant.

Number of Participants (Planned):

Approximately 210

Diagnosis and Main Criteria for Study Participation

Healthy males and females aged 18 to 45 years (inclusive) with no prior history of anthrax disease, suspected exposure to anthrax, or vaccination with anthrax vaccine and no history of allergic reaction or intolerance to quinolone or tetracycline antimicrobials and as determined by inclusion and exclusion criteria listed below.

Inclusion Criteria

Individuals must meet all of the following inclusion criteria for study participation:

1. Written informed consent obtained from the participant (dated, signed, and captured in the medical chart at the site).
2. A male or female, aged 18 to 45 years of age, inclusive, at the time of informed consent.
3. Healthy condition as established by medical history and clinical examination before entering into the study.

[redacted]

4. Have a body mass index (BMI) less than or equal to 35.0 kg/m^2 at the Screening visit.
5. Have adequate venous access for phlebotomies.
6. For a woman of childbearing potential (WOCBP), negative pregnancy test at Screening and pre-randomization on Day 1, not currently breastfeeding, and no intention to become pregnant during the study period through 12 months after last receipt of any investigational product (IP).

   Every female participant is considered to be a WOCBP unless she is surgically sterile (ie, has had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy) or postmenopausal [which is defined as >12 consecutive months without menses and a Screening FSH of >30 mIU/mL]. Adequate birth control (as defined here) must be initiated at least one month prior to randomization on Day 1 and used throughout the trial. Adequate birth control methods are sexual abstinence, intrauterine device/system (IUD/IUS), birth control pills, implantable or injectable contraceptives (eg, Norplant® or Depo-Provera®), removable birth control device (eg, NuvaRing® or Evra® patches) or double-barrier method of birth control (diaphragm in combination with contraceptive jelly or condoms in conjunction with contraceptive jelly, cream or foam), tubal ligation, or have a monogamous relationship with vasectomized partner who has been vasectomized for 6 months or more prior to the participant's trial entry.

   Female participants randomized to Groups 1 or 2: be willing to add a double-barrier method, IUD, or abstinence as back-up forms of birth control since ciprofloxacin and doxycycline may decrease the effectiveness of birth control pills, implantable or injectable contraceptives.

Exclusion Criteria

Individuals meeting any of the following exclusion criteria will be excluded from study participation:

1. A Screening clinical laboratory test result greater than the central laboratory's upper limit of normal (ULN) for aspartate aminotransferase (AST), alanine aminotransferase (ALT), random glucose, total bilirubin, blood urea nitrogen (BUN), or creatinine. Other serum chemistry parameters that are not within the reference range will not be considered exclusionary, unless deemed clinically significant by the principal investigator.
2. History of allergic reaction or intolerance to quinolone antimicrobials or any medical condition that would contraindicate the use of ciprofloxacin, including and not limited to vascular disorders, tendon disorders, certain genetic connective tissue disorders (eg, Marfan and Ehlers–Danlos syndrome), prolongation of QT interval, seizures, peripheral neuropathy, increased risk of *C. difficile* infection (see ciprofloxacin prescribing information in the Pharmacy Manual).

[redacted]

3. History of allergic reaction or intolerance to tetracycline antibiotics or any medical condition that would contraindicate the use of doxycycline including an increased risk of *C. difficile* infection, increases in BUN or an increased sensitivity to direct sunlight or ultraviolet radiation resulting in erythema (see doxycycline prescribing information in the Pharmacy Manual).
4. Has a need for any of the prohibited medications in Section 6.5.1 or requires the medications/foods within the prohibited times in Section 5.3.1.1.
5. Have a tattoo/scar/birthmark or any other skin condition affecting the deltoid area that may interfere with injection site assessments.
6. History of anthrax disease, suspected exposure to anthrax, or previous vaccination with any anthrax vaccine.
7. Have previously served in the military any time after 1990 or plan to enlist in the military any time from Screening through the final telephone contact.
8. Previous anaphylactic reaction, severe systemic response, or serious hypersensitivity to a prior immunization or a known allergy to synthetic ODNs, aluminum, formaldehyde, benzethonium chloride (phemerol).
9. Plan to have an elective surgery at any point during the study until after the final safety phone contact.
10. Have donated or plan to donate blood within one month prior to enrollment or at any point during the study until after the final safety phone contact.
11. Use of any investigational or non-registered product (drug, vaccine or biologic) within 30 days preceding the dose of study vaccine, or planned use during the study until after the final safety phone contact.
12. Planned administration of any commercially-available vaccine from one week prior to the first study vaccination through two weeks after the last vaccination.
13. Have experienced chronic dosing (defined as more than 14 days) with any immune-modifying drugs within six months of study enrollment. This includes oral, intramuscular, intra-articular, intravenous, or inhalation corticosteroids except in the case of inhaled or intranasal medications for seasonal allergies (see Table 3).
14. Receipt of immunoglobulins and/or any blood products within the three months preceding study enrollment or at any point during the study period until after the final safety visit on Day 51.
15. An abnormal electrocardiogram (ECG) at screening interpreted as ‘Abnormal, Significant’. Inclusion of participants with ‘Abnormal, Insignificant’ ECGs will be based on the principal investigator’s discretion.
16. Have an active malignancy or history of metastatic or hematologic malignancy.

[redacted]

17. Have a history of an autoimmune, inflammatory, vasculitic or rheumaticor rheumatic disease including but not limited to systemic lupus erythematosus, Guillain-Barré syndrome, myasthenia gravis, polymyalgia rheumatica, diabetes mellitus type I, rheumatoid arthritis or scleroderma.
18. A positive laboratory evidence of hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) HIV-1 or HIV-2 infection.
19. Positive result on urine drug screen, any evidence of ongoing drug abuse or dependence (including alcohol), or recent history (over the past five years) of treatment for alcohol or drug abuse.
20. Has an acute disease at the time of enrollment.

    Note that screening lab tests may be delayed to allow the resolution of a transient acute condition or the subject may be rescreened according to procedures under Section 5.4.
21. Any medical condition that, in the opinion of the investigator, could adversely impact the participant's involvement or the conduct of the study.
22. Have a significant chronic condition (see Sponsor's guidance on significant chronic conditions in Appendix C), eg, serious cardiovascular, pulmonary, hepatic, type II diabetes mellitus or renal disease that, in the opinion of the investigator, would render treatment unsafe or would interfere with trial evaluations or completion of the study.
23. An opinion of the investigator that it would be unwise to allow the participant to be randomized into the study.
24. Member or immediate family member of an investigator site team.

Investigational Products (IP), Dosage, Schedule and Mode of Administration:

- AV7909 (containing 0.5 mL AVA + 0.25 mg CPG 7909 adjuvant per dose) will be administered IM in the deltoid muscle of alternating arms to all (Groups 1 to 3) on Day 8 and Day 23.
- Ciprofloxacin (500 mg po q 12 hr) will be administered to participants in Group 1 on Days 4-9, Days 22-24, and Days 31-37.
- Doxycycline (100 mg po q 12 hr) will be administered to participants in Group 2 on Days 2-9, Days 22-24, and Days 32-38.

Duration of Treatment:

All participants will receive two vaccinations with AV7909 two weeks apart.

Participants in Group 1 will be intermittently dosed with ciprofloxacin over 33 days and participants in Group 2 will be intermittently dosed with doxycycline over 36 days.

Endpoints

[redacted]

Primary Endpoints:

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

Secondary Endpoints:

Safety

- Incidence of AEs from the first dose of any IP through the Final Study Visit (Day 51 ± 1 d)
- Incidence of serious AEs (SAEs) from the first dose of any IP until the 12-month follow-up (Day 388 ± 14d)
- Incidence of solicited systemic and injection site reactions reported in participant e-diaries following each vaccination
- Incidence of AESIs from the first dose of any IP until the 12-month follow-up (Day 388 ± 14 d)
- Incidence of clinical laboratory abnormalities

Pharmacokinetics and Immunogenicity

- AUC_{0-12h} and C_{max} for ciprofloxacin on Days 4 and 31 and for doxycycline on Days 2 and 32
- Geometric mean TNA 50% neutralizing factor (NF_{50}) values 2 weeks after the second vaccination (Day 37 ± 1 d)

Statistical Methods:

Statistical Analysis

To characterize the PK profiles of ciprofloxacin and doxycycline, the following PK parameters will be calculated using noncompartmental analytic methods:

- Maximum observed concentration: C_{max}
- Time of C_{max}: t_{max}
- Elimination half-life: $t_{1/2}$
- Elimination rate constant: K_{el}
- Area under the serum concentration-time curve (12 hours): AUC_{0-12h}
- Area under the first moment curve: AUMC
- Mean residence time: MRT
- Area under the serum concentration-time curve extrapolated to infinity: AUC_{0-inf}

Effect of AV7909 on Ciprofloxacin Pharmacokinetics

[redacted]

To examine the effect of AV7909 vaccination on the steady state pharmacokinetics of ciprofloxacin, the trough values for Days 4 through 8 and Days 31 through 35 will be analyzed to demonstrate that ciprofloxacin concentrations have achieved steady state on Day 8 and Day 35. Then the C_{max} and $AUC_{0\text{-}12h}$ values for ciprofloxacin determined for Group 1A participants on Day 35 (following two doses of AV7909) will be compared to those determined on Day 8 (prior to AV7909 vaccination). Point estimates and 90% confidence intervals (CIs) will be calculated for the geometric mean ratios. If the CIs are all within 0.80 and 1.25, then it can be concluded that AV7909 vaccination does not significantly influence the steady state C_{max} and $AUC_{0\text{-}12h}$ values of ciprofloxacin.

Effect of AV7909 on Doxycycline Pharmacokinetics

To examine the effect of AV7909 vaccination on the steady state pharmacokinetics of doxycycline, the trough values for Days 2 through 8 and Days 32 through 38 will be analyzed to demonstrate that doxycycline concentrations have achieved steady state on Day 8 and Day 38. Then the C_{max} and $AUC_{0\text{-}12h}$ values for doxycycline determined for Group 2A participants on Day 38 (following two doses of AV7909) will be compared to those determined on Day 8 (prior to AV7909 vaccination). Point estimates and 90% CIs will be calculated for the geometric mean ratios. If the CIs are all within 0.80 and 1.25, then it can be concluded that AV7909 vaccination does not significantly influence the steady state C_{max} and $AUC_{0\text{-}12h}$ values of doxycycline.

For the secondary endpoints, a similar comparison will be conducted for the C_{max} and $AUC_{0\text{-}12h}$ values for ciprofloxacin from Day 31 vs Day 4 to determine if these single-dose PK values of ciprofloxacin are affected by AV7909 vaccination and a similar comparison will be conducted for the C_{max} and $AUC_{0\text{-}12h}$ values for doxycycline from Day 32 vs Day 2 to determine if these single-dose PK values of doxycycline are affected by AV7909 vaccination.

Effect of Ciprofloxacin or Doxycycline on AV7909 Immunogenicity

To evaluate whether the administration of ciprofloxacin affects the immunogenicity of AV7909, TNA NF_{50} values two weeks after the second dose of AV7909 will be compared between the cohort of participants that received both ciprofloxacin and AV7909, ie, Group 1, also known as the ciprofloxacin test cohort, and the cohort who received AV7909 only, ie, Group 3 or the reference cohort. Point estimates and two-sided 95% lower CIs will be constructed for the ratio (test: reference) of geometric means. If the lower bound of the two-sided 95% lower CI is greater than 0.5 (the non-inferiority margin) it can be concluded that the immune response in the cohort who received AV7909 plus ciprofloxacin is non-inferior to the cohort which received AV7909 alone and thus that ciprofloxacin did not demonstrably affect the immunogenicity of AV7909.

The same evaluation will be conducted to determine if the administration of doxycycline affects the immunogenicity of AV7909 in that TNA NF_{50} values two weeks after the second dose of AV7909 will be compared between the cohort of participants that received both doxycycline and AV7909, ie, Group 2, the doxycycline test cohort, and the cohort who received AV7909 only (ie, Group 3 or the reference cohort). Point estimates and two-sided 95% lower CIs will be constructed for the ratio (test: reference) of geometric means. If the

[redacted]

lower bound of the two-sided 95% lower CI is greater than 0.5 (the non-inferiority margin) it can be concluded that the immune response in the cohort who received AV7909 plus doxycycline is non-inferior to the cohort which received AV7909 alone and thus that doxycycline did not demonstrably affect the immunogenicity of AV7909.

Sample Size Considerations

Antibiotic PK: Assessment of the effect of vaccination with AV7909 on the PK of either antibiotic will be made using the geometric mean of the within-participant ratio of C_{max} and $AUC_{0\text{-}12h}$ for either ciprofloxacin or doxycycline before (Day 8) vs after (Day 35 or Day 38) AV7909 vaccination. The equivalence (no interaction) margin for the ratio is [0.80, 1.25], which will be compared with the 90% CI for the geometric mean ratio. Assuming that the coefficient of variation (CV) with the within-participant ratio is 30% and the true ratio is 0.95, 27 participants allows for 90% power at significance level 0.05 while 34 participants would provide 95% power. A group size of 40 participants in each of the antibiotic PK groups (Group 1A and Group 2A) is planned to allow for up to 30% participants being excluded from the PK population.

Immunogenicity: Sample sizes of 53 in each cohort (AV7909 alone vs AV7909 + antibiotic [either ciprofloxacin or doxycycline]) provide 90% power at the 2.5% one-sided significance level for the non-inferiority test (defined as the lower bound of the two-sided 95% CI of the ratio greater than 0.5), if the true ratio of geometric means is 0.85 and the CV of NF_{50} values between participants in the same group is 100%. A cohort size of 70 is planned to allow for up to 25% of participants to be excluded from the immunogenicity population.

[redacted]

2. INTRODUCTION

2.1. Study Rationale

Antimicrobial therapy is an important component of post-exposure prophylaxis (PEP) following exposure to aerosolized *Bacillus anthracis* spores. According to the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommendations for PEP of inhalation anthrax, BioThrax® (Anthrax Vaccine Adsorbed; AVA) administered subcutaneously at 0, 2, and 4 weeks, combined with appropriate antimicrobial therapy, is currently licensed for this indication in previously unvaccinated adults {Wright et al, 2010}. While a two-dose vaccination schedule with AV7909 for PEP would have clear logistical advantages over the three-dose schedule with BioThrax, antimicrobial therapy would still be a required component of the PEP schedule. The purpose of this study is to identify any potential effects of AV7909 vaccination on the PK of the antibiotics ciprofloxacin or doxycycline and any potential effects of ciprofloxacin or doxycycline therapy on the immunogenicity of AV7909. Both ciprofloxacin and doxycycline have been chosen for use in this study because they are first-line therapies recommended by the ACIP for PEP {Wright et al, 2010}.

2.2. Background

Anthrax is an acute non-communicable infectious disease caused by *B. anthracis,* a spore-forming, gram-positive bacterium that occurs globally {Brachman et al, 2008; WHO, 2008}. While human cases are rare in the United States (US), the bioterrorist use of *B. anthracis* spores as a biological weapon resulted in the exposure of tens of thousands of individuals across six states and the District of Columbia in 2001 {CDC, 2001}. The CDC considers *B. anthracis* to be one of the most likely biological agents to be used in any future terrorism activities {CDC, 2014}.

While vaccination prior to exposure offers the optimal protection against anthrax, mass vaccination is neither practical nor feasible as a defense against bioterrorism {CDC, 2000}. At the time of the bioterrorist events in 2001, the only Food and Drug Administration (FDA)-approved post-exposure treatments for anthrax were the antimicrobials: ciprofloxacin, ofloxacin, doxycycline, penicillin VK and amoxicillin {CDC, 2000}. In the event of an aerosol exposure, the CDC's ACIP recommended at the time that PEP consist of a minimum of 30 days of antibiotics and possibly a longer course of 42-60 days. The ACIP recommendations from 2000 also stated that if a vaccine was available, three doses of vaccine should be administered (at 0, 2, and 4 weeks) with discontinuation of antibiotic after the third vaccination {CDC, 2000}.

In response to the 2001 attacks, approximately 9300 individuals were initially prescribed antimicrobial prophylaxis for at least 60 days; however, a subsequent study determined that compliance with this schedule was poor. Based on interviews with 6178 persons, 86% (n=5343) took at least one dose of antimicrobial prophylaxis but fewer than half (44%, n=2712) reported taking antimicrobial prophylaxis for at least 60 days {Shepard et al, 2002}.

[redacted]

The CDC subsequently offered an additional antimicrobial treatment in a voluntary treatment continuation program with or without three doses of the BioThrax vaccine; about 200 opted to receive the supply of antimicrobials plus three doses of BioThrax {Tierney et al, 2003}.

Ultimately, the attacks resulted in 22 cases of anthrax; 11 cutaneous and 11 inhalation, five of which (all inhalation cases) resulted in mortality {Jernigan et al, 2002}. No cases of anthrax were identified among persons recommended to take antimicrobial prophylaxis after the bioterrorist attacks of 2001 {Tierney et al, 2003}.

In November of 2015, the FDA approved BioThrax for PEP given in three doses (administered at 0, 2, and 4 weeks) along with a post-exposure regimen of appropriate antimicrobial prophylaxis. {Wright et al, 2010} However, in contrast to the ACIP's earlier recommendation, which indicated that antimicrobial prophylaxis could cease after the third dose of vaccine {CDC, 2002}, the ACIP updated their recommendations to reflect a 60-day antimicrobial treatment period and to continue with the antimicrobial for 14 days following the third dose of vaccine, which could result in the antimicrobial being used for more than 60 days, if the initiation of the vaccination series was delayed.

Given the poor compliance with an antimicrobial regimen of 60 days as observed in 2001, there is a demonstrated medical need for a vaccine that can induce a rapid and robust immune response. AV7909, a vaccine consisting of AVA plus the adjuvant CPG 7909, is under development to meet this need. CPG 7909 is a synthetic immunostimulatory oligonucleotide (short DNA sequence). It has been shown to be a toll-like receptor 9 (TLR9) agonist that induces both an enhanced antigen-specific antibody response and a natural killer (NK) T-cell immune response when used in combination with prophylactic (preventative) or therapeutic vaccines {Krieg, 1996; Pisetsky, 1996; Kim et al, 1999; Stewart et al, 2008}.

By combining AVA with CPG 7909, the AV7909 product development program aims to create a new vaccine that will accelerate the development of the immune response to the *B. anthracis* antigens, reducing the number of doses required to induce full protection, thereby reducing the amount of antigen required to establish protective immunity. From the three clinical studies conducted to date, Study V011, Study EBS.AVA.201 and Study EBS.AVA.208 {Rynkiewicz et al, 2011; Hopkins et al, 2013; Hopkins et al, 2016}, a formulation consisting of 0.5 mL of AVA plus 0.25 mg CPG 7909 administered intramuscularly (IM) on a 0, 2 week schedule has been selected as the candidate formulation for Phase 3.

Based on the results of the last study, vaccination of healthy adults with 2 doses of AV7909 can potentially accelerate the development of a protective level of immunity by one or two weeks (in comparison to the time required with the 3-dose schedule of BioThrax) depending on whether AV7909 doses are administered four weeks or two weeks apart {Hopkins et al, 2016}. This study also demonstrated that AV7909 given in a 3-dose schedule (as per the BioThrax label) resulted in a greater percentage of individuals achieving a potentially protective antibody level one week after the last vaccination and at all subsequent time points evaluated.

A clinical trial conducted with BioThrax and ciprofloxacin {EPDG, 2014} as part of the process of PEP licensure found no evidence of any interaction between vaccination with BioThrax and the pharmacokinetics (PK) of ciprofloxacin or between dosing with ciprofloxacin and the immunogenicity of BioThrax. It is the goal of this trial to demonstrate that vaccination with

[redacted]

AV7909 does not affect the PK profiles of either ciprofloxacin or doxycycline and that neither ciprofloxacin nor doxycycline impair the immunogenicity of AV7909.

2.3. Benefit/Risk Assessment

2.3.1. Benefits

No benefits can be guaranteed to individuals participating in this study. However, by joining this study, participants will be contributing to research that may result in the licensure of the next generation anthrax vaccine for PEP (ie, AV7909).

2.3.2. Risks

2.3.2.1. BioThrax

More than 14 million doses of BioThrax have been administered to over 3.3 million people since it was approved in the U.S. in 1970 for pre-exposure prophylaxis {BioThrax.com }. BioThrax is approved by the Food and Drug Administration (FDA) and indicated for active immunization for the prevention of disease caused by *B. anthracis* in persons 18 through 65 years of age. Details with respect to the potential risks of administration of BioThrax can be found in the BioThrax prescribing information {BioThrax® Prescribing Information, 2015}. The most common injection-site reactions observed in clinical studies included tenderness, pain, erythema/redness, edema/swelling, and arm motion limitation. The most common systemic reactions were muscle aches, fatigue, and headache. Other side effects included bruising, warmth, itching, or nodules at the injection site, nasopharyngitis, back pain, nausea and diarrhea. See the AV7909 Investigator's Brochure for more information.

In a 200-person trial designed to evaluate the BioThrax PEP schedule, the most common solicited injection site reactions were lump, tenderness and erythema, and the common systemic reactions were fatigue, headache and myalgia. Of those individuals who reported solicited reactions, ≥ 98% percent required minimal to no treatment and reported little to no interference with activities of daily living {BioThrax® Prescribing Information, 2015}.

2.3.2.2. CPG 7909

CPG 7909 has been investigated clinically since the mid-1990s for indications that have included cancer monotherapy, combination use with anti-cancer therapies, and as an adjuvant in vaccines against infectious diseases and cancers. The most relevant risk data for this trial come from clinical studies of CPG 7909 used as an adjuvant in vaccine trials for hepatitis B, influenza, anthrax, malaria, gram negative sepsis, pneumococcal disease, and cytomegalovirus in normal participants. Safety data from such trials indicated that the most commonly reported reactogenicities were increases in the frequency and severity of injection site reactions and systemic AEs including fatigue, headache, flu-like symptoms, transient decreases in neutrophil and lymphocyte counts, and myalgia have been reported with the addition of CPG 7909 to vaccine antigens {Coley, 2006; Cooper et al, 2004; Sagara et al, 2009; Mullen et al, 2008}.

While immune activation by CPG 7909 is designed to be transient and localized to vaccine-exposed draining lymphatics, the possibility exists for pathologic and sustained non-specific

[redacted]

activation of either T or B lymphocytes. Because of the potential for CpG ODN adjuvants to trigger autoimmune disease in susceptible individuals {Segal et al, 2000}, all participants should be monitored for a minimum of 12 months after the last vaccination. Participants who discontinue study treatment should be encouraged to attend all subsequent clinic visits and safety follow-up contacts to facilitate this monitoring. See the Investigator's Brochure for additional details on the relationship of CPG 7909 to adverse events of special interest (AESIs; events with autoimmune etiology).

2.3.2.3. AV7909

The risks associated with AV7909 are similar to those described for BioThrax and CPG 7909 since AV7909 is a combination of the two products. In the three clinical trials completed to date as a part of the AV7909 clinical development program, 241 healthy participants were immunized with the combination of AVA + CPG 7909. Across these three trials, most participants have experienced mild to moderate injection site reactions following vaccination with between 40% and 90% of participants reporting tenderness, pain, and arm motion limitation in their diary responses. Participants reporting these latter reactions experienced predominantly mild reactions, with generally less than 10% experiencing moderate or severe reactions. The most common systemic adverse reactions (observed in ≥5% of participants) were muscle aches, fatigue, and headache. See the AV7909 Investigator's Brochure for more information.

Hypersensitivity and Anaphylactic/Anaphylactoid Reactions

Acute allergic reactions have occurred in the AV7909 program with a report of urticaria after the second of two 0.5 mL doses of AV7909 (AV7909 Arm 1; Study EBS.AVA.208) that resolved with diphenhydramine hydrochloride. This arm received two doses of AV7909 containing 0.5 mL AVA +0.25 mg CPG 7909 given 2 weeks apart {Hopkins et al, 2016}. The participant had a history of urticaria and this event was considered by the investigator as unrelated to the study product administration. In Study EBS.AVA.201, urticaria was reported in a participant in the AV7909 Formulation 1 arm, which was treated and resolved after 2 days and considered possibly related to study product administration. The Formulation 1 arm participants received two 0.5 mL doses formulated to contain 0.5 mL AVA + 0.5 mg CPG 7909 that were delivered IM two weeks apart.

Two participants in Study EBS.AVA.208 discontinued vaccination because of mild generalized pruritus and rash (AV7909 Arm 2) and moderate rash (AV7909 Arm 1), all events considered to be related to study product administration. Both Arm 1 and Arm 2 received two doses of AV7909 containing 0.5 mL AVA + 0.25 mg CPG 7909; however, for Arm 1, the doses were delivered two weeks apart and for Arm 2, the doses were delivered 4 weeks apart {Hopkins et al, 2016}. In Study V011, which consisted of three treatment groups [AVA (0.5 mL) alone, CPG 7909 (1.0 mg)-alone and AVA (0.5 mL) + CPG 7909 (1.0 mg)] all administered as three doses two weeks apart, two participants in the AVA + CPG 7909 arm had hypersensitivity reactions. Both of these were considered by the investigator to be unlikely related to study product administration. An additional participant in the AVA + CPG 7909 group discontinued vaccination after the second injection due to the development of moderate generalized rash (accompanied by pruritus) that was considered to be related to study product administration {Coley, 2006}. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

[redacted]

AV7909 is not to be administered to participants with known sensitivity to any of the vaccine components, eg, synthetic ODNs, formaldehyde, benzethonium chloride (phemerol), or aluminum, or a sensitivity to latex.

No participants in the completed AV7909 clinical trials or in CPG 7909-adjuvanted infectious disease trials have reported AEs related to autoimmune disorders, although several have reported positive, transient and/or non-symptomatic findings for clinical laboratory markers of disease such as anti-nuclear antibodies (ANA), anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies, and rheumatoid factor (RF). In oncology trials of CPG 7909 (reviewed in the AV7909 Investigator's Brochure) that typically use higher doses and treatment durations than expected with AV7909 vaccine exposure, autoimmune disease has been reported in multiple participants, although causal attribution to the study product is complicated by comorbidities and concomitant products/therapies. Autoimmune conditions have included polyarthralgia, arthritis, Sjögren's syndrome, autoimmune thyroiditis, vitiligo, Guillain-Barré syndrome, and ulcerative colitis.

2.3.2.4. Study Procedures (IM injections and Venipuncture)

Potential risks associated with IM injections include accidental injection of a vein instead of muscle, dizziness, fainting, or infection, as well as pain associated with a needle stick. Potential risks associated with venipuncture include pain, bruising, dizziness, and infection.

2.3.2.5. Ciprofloxacin

Ciprofloxacin, a fluoroquinolone antimicrobial agent, belongs to the class of quinolone antibiotics which target bacterial DNA gyrase and topoisomerase IV. The fluoroquinolones including ciprofloxacin have potent bactericidal activities against a broad range of gram-negative and gram-positive bacteria including *B. anthracis* {MacDougall, 2018}.

Fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together including:

- Tendinitis and tendon rupture
- Peripheral neuropathy
- Central nervous system effects

For additional safety information on ciprofloxacin, please refer to the prescribing information provided in the Pharmacy Manual.

2.3.2.6. Doxycycline

Doxycycline hyclate is a broad-spectrum antibiotic synthetically derived from oxytetracycline. As a member of the tetracycline class of antibiotics, doxycycline functions primarily through a bacteriostatic mechanism which is thought to occur via the inhibition of protein synthesis. The tetracyclines, including doxycycline, are active across a broad range of gram negative and gram-positive bacteria including *B. anthracis.* Details with respect to the potential risks associated with the administration of doxycycline hyclate can be found in the prescribing information provided in the Pharmacy Manual.

[redacted]

3. STUDY OBJECTIVES & ENDPOINTS

3.1. Study Objectives

3.1.1. 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.

3.1.2. 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.

3.2. Study Endpoints

3.2.1. Primary Endpoints

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

3.2.2. Secondary Endpoints

Safety

- Incidence of AEs from the first dose of any IP through the Final Study Visit (Day 51 ± 1 d)
- Incidence of serious AEs (SAEs) from the first dose of any IP until the 12-month follow-up (Day 388 ± 14 d)
- Incidence of solicited systemic and injection site reactions reported in participant e-diaries following each vaccination
- Incidence of AESIs from the first dose of any IP until the 12-month follow-up (Day 388 ± 14 d)
- Incidence of clinical laboratory abnormalities

Pharmacokinetics and Immunogenicity

- $AUC_{0\text{-}12h}$ and C_{max} for ciprofloxacin on Days 4 and 31 and for doxycycline on Days 2 and 32
- Geometric mean TNA 50% neutralizing factor (NF_{50}) values 2 weeks after the second vaccination (Day 37 ± 1 d)

[redacted]

4. STUDY DESIGN

4.1. Overall Study Design

This is a randomized, open-label, phase 2, multicenter trial to investigate the potential interactions of AV7909 and ciprofloxacin or doxycycline when administered concomitantly. The potential effect of AV7909 vaccination on ciprofloxacin or doxycycline serum levels will be investigated by evaluating the changes in the single dose and steady-state PK profiles of ciprofloxacin or doxycycline before and after vaccination with a two-dose series of AV7909. The effect of ciprofloxacin or doxycycline dosing on the immunogenicity of AV7909 will be investigated by evaluating whether TNA levels two weeks following the final dose of a two-dose vaccination series is affected by concomitant dosing with oral ciprofloxacin or doxycycline.

Healthy males and females 18 to 45 years of age, inclusive, will read, sign and date an informed consent form (ICF) explaining the study and then be screened (2 to 28 days prior to randomization) for eligibility to participate in the study. Participants (N=210) meeting the entry criteria will be evenly randomized 1:1:1 to one of the three investigational product (IP) groups shown in Table 2. Approximately the first 40 participants who are randomized into IP Groups 1 and 2 will be assigned to Treatment Groups 1A or 2A while the remaining 30 participants randomized into IP Groups 1 and 2 thereafter will be assigned to Treatment Groups 1B or 2B.

Randomization will be stratified by site. A representative racial distribution will be sought among participants and sites will be asked to recruit populations that are gender- and age-balanced (ie, between 40-60% male with 40-60% of participants in the two age ranges of 18-30 years of age and 31-45 years of age).

Table 2: Study Groups

IP Group	Treatment Group	Treatment	Sample Size (N)	
1 Cipro	1A	AV7909 + ciprofloxacin (with PK assessment)	≈40	≈70
	1B	AV7909 + ciprofloxacin (without PK assessment)	30	
2 Doxy	2A	AV7909 + doxycycline (with PK assessment)	≈40	≈70
	2B	AV7909 + doxycycline (without PK assessment)	30	
3 AV7909	3	AV7909 only	70	
		TOTAL	≈210	

Figure 1 shows the design for this study, with an event schematic for the entire study being presented in Figure 2 followed by brief discussions of each group's schedule. Detailed schedules are presented in Section 8.1.2 through Section 8.1.6.

Safety in all groups will be assessed up to Day 51 by in-clinic recording of vital signs, adverse events (AEs, SAEs, and potential AESIs), concomitant medications, physical examination results, and by clinical laboratory outcomes recorded at screening and at Day 51 or the Early Withdrawal Visit (EWV), if applicable. Adverse events of special interest are AEs associated with autoimmune disease as defined by the Center for Biologics Evaluation and Research

[redacted]

(CBER); refer to Appendix B; these may represent a safety signal for vaccine-associated autoimmunity. The severity of AEs, laboratory test results for select analytes, and vital sign results will be assessed based on the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* (refer to Appendix A).

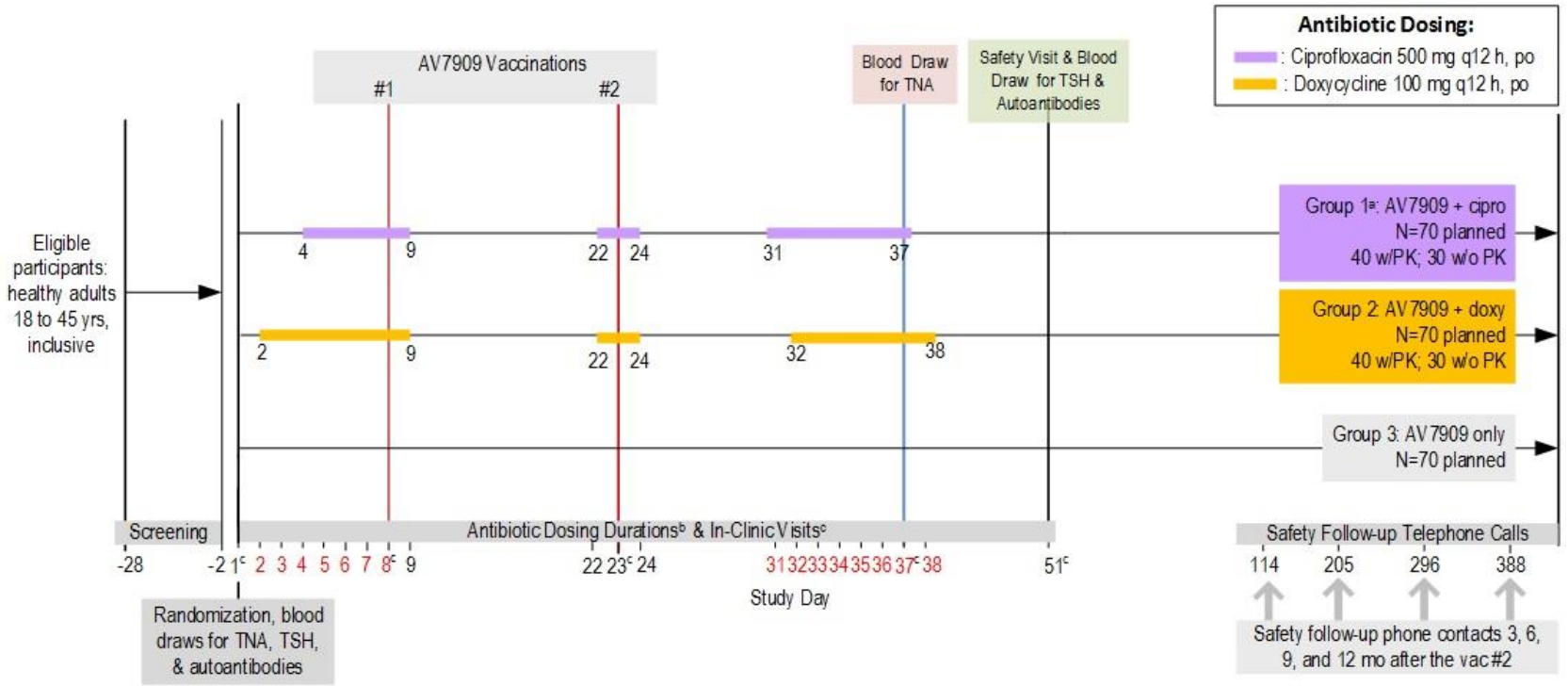
Additionally, an electronic diary (e-diary) will be used following each vaccination to collect daily information on reactogenicity events including systemic and local (injection site) reactions and any changes in concomitant medications. For participants in Group 1 and 2, a separate antibiotic compliance e-diary will be used to record the dates and times of self-administered ciprofloxacin or doxycycline doses. This information will be evaluated on a routine basis and used by the site staff to identify additional AEs, SAEs, potential AESIs, and changes in concomitant medications as well as to document ciprofloxacin or doxycycline compliance. Blood samples for autoimmunity assessment will be taken at randomization (Day 1) and Day 51 (or EWV) for testing (if medically indicated as per PI's discretion based on report of potential AESI) of TSH levels, and RF, ANA and anti-dsDNA autoantibodies.

Safety follow-up phone contacts to collect information on SAEs and any potential AESIs will occur 3 months (Day 114 ± 14 d), 6 months (Day 205 ± 14 d), 9 months (Day 296 ± 14 d) and 12 months (Day 388 ± 14 d) after the second vaccination. Samples may also be collected at unscheduled visits following the safety follow-up phone contact(s) to investigate reports of potential AESIs.

Independent safety oversight will be provided by a Data Safety Monitoring Board (DSMB), which will be notified of significant AEs (refer to Section 8.5) as determined by the medical monitor (MM) on an ongoing basis. The DSMB will comprise at least three voting members, to include one expert in immunology to specifically support the evaluation of potential AESIs for autoimmune etiology, if pre-existing or new onset, and relationship to the study product. The DSMB will make recommendations regarding the safety of continuing enrollment and dosing. Study enrollment and dosing may be interrupted at the request of the DSMB Chair if it is believed that an AE represents a significant safety concern requiring suspension of dosing pending full DSMB evaluation. The operations of the DSMB will be detailed in a DSMB Charter.

[redacted]

Figure 1: Study Design for EBS.AVA.210



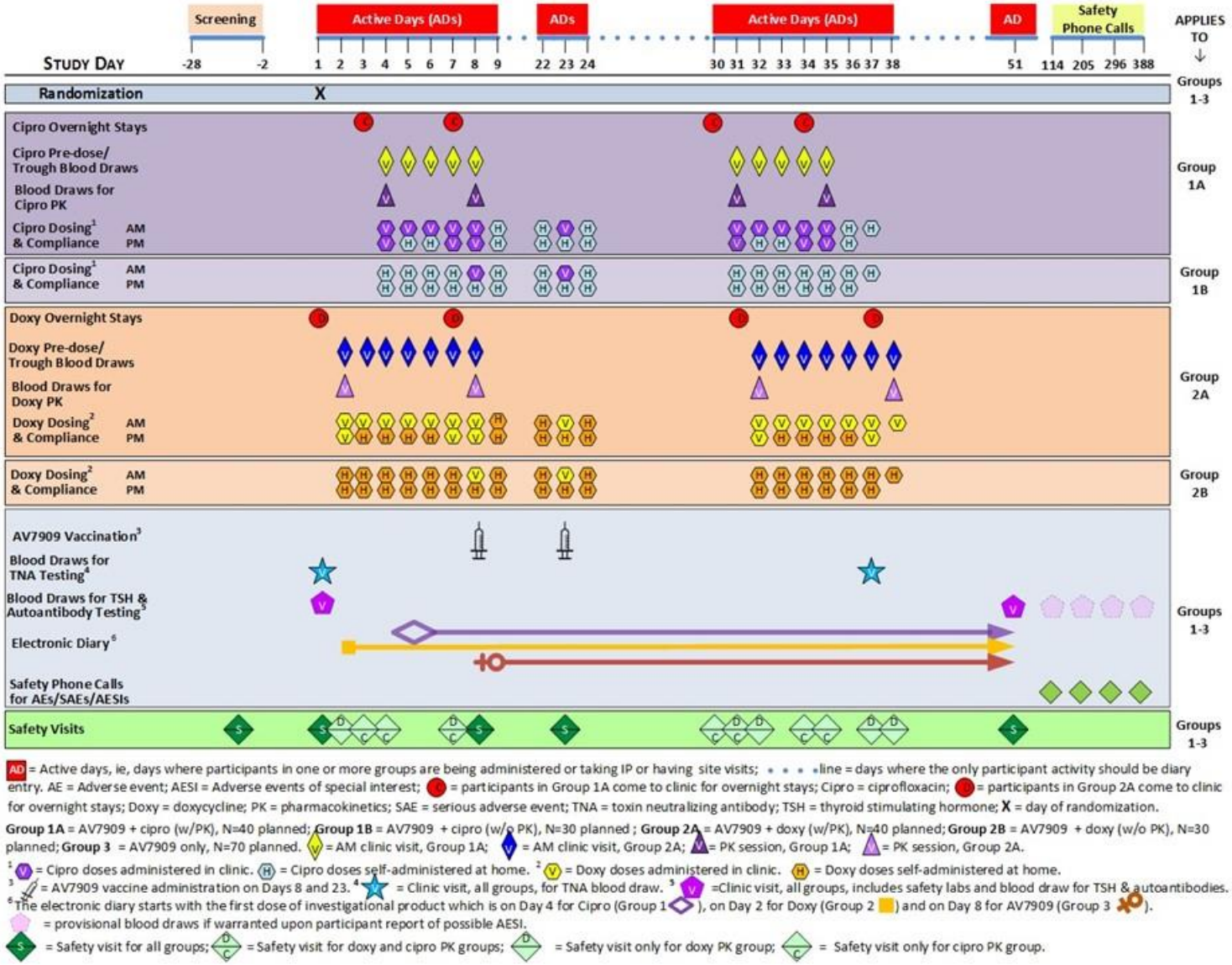
cipro = ciprofloxacin; doxy = doxycycline; PK = pharmacokinetics; po = per os, (oral); q12 h = every 12 hours; TNA = toxin-neutralizing antibody; TSH = thyroid-stimulating hormone

[a]In Group 1, the evening dose on Day 37 is not administered. [b]Antibiotic dosing for Groups 1 & 2 up to Day 8 is to enable 2 PK sessions prior to vaccination #1 (vac #1) on Day 8. Dosing continues on Day 9, extends around vac #2 (on Days 22 to 24) and then discontinues until Day 31 (cipro) or Day 32 (doxy). Cipro dosing continues from Day 31 to Day 37 and doxy dosing continues from Day 32 to Day 38, encompassing 2 PK sessions after the complete vaccination regimen as well as the blood draw for TNA. [c]Solid lines at Days 1, 8, 23, 37 and 51 are days when all groups have in-clinic visits. Days in red are those when Groups 1A and/or 2A have clinic visits for blood draws for pre-dose, trough values or PK.

All visits are performed on an outpatient basis, except Groups 1A and 2A participants will be admitted to the clinic in the evening for an overnight stay on days preceding serial (all day) blood collections needed for determination of cipro or doxy concentrations. For Group 1A, those samples will be taken on Days 4, 8, 31, and 35; for Group 2A, those samples will be taken on Day 2, 8, 32, and 38. AV7909 vac #1 will be administered to all groups on Day 8. For Groups 1B, 2B, and 3, it will be their first clinic visit after randomization and for Groups 1A and 2A, vaccination will occur in the evening following the second PK session. AV7909 vac #2 will be administered on Day 23. The final blood draw for TNA will be on Day 37 for all groups. There will be a final visit for safety for all groups on Day 51, four weeks after the last dose of AV7909, which is when the final blood draw for TSH & autoantibodies will also be collected.

[redacted]

Figure 2: Event Schematic for EBS.AVA.210 Groups 1 to 3



AD = Active days, ie, days where participants in one or more groups are being administered or taking IP or having site visits; • • • line = days where the only participant activity should be diary entry. AE = Adverse event; AESI = Adverse events of special interest; = participants in Group 1A come to clinic for overnight stays; Cipro = ciprofloxacin; = participants in Group 2A come to clinic for overnight stays; Doxy = doxycycline; PK = pharmacokinetics; SAE = serious adverse event; TNA = toxin neutralizing antibody; TSH = thyroid stimulating hormone; X = day of randomization.

Group 1A = AV7909 + cipro (w/PK), N=40 planned; **Group 1B** = AV7909 + cipro (w/o PK), N=30 planned ; **Group 2A** = AV7909 + doxy (w/PK), N=40 planned; **Group 2B** = AV7909 + doxy (w/o PK), N=30 planned; **Group 3** = AV7909 only, N=70 planned. = AM clinic visit, Group 1A; = AM clinic visit, Group 2A; = PK session, Group 1A; = PK session, Group 2A.

[1] = Cipro doses administered in clinic. = Cipro doses self-administered at home. [2] = Doxy doses administered in clinic. = Doxy doses self-administered at home.

[3] = AV7909 vaccine administration on Days 8 and 23. [4] = Clinic visit, all groups, for TNA blood draw. [5] =Clinic visit, all groups, includes safety labs and blood draw for TSH & autoantibodies.

[6] The electronic diary starts with the first dose of investigational product which is on Day 4 for Cipro (Group 1), on Day 2 for Doxy (Group 2) and on Day 8 for AV7909 (Group 3).

= provisional blood draws if warranted upon participant report of possible AESI.

= Safety visit for all groups; = Safety visit for doxy and cipro PK groups; = Safety visit only for doxy PK group; = Safety visit only for cipro PK group.

[redacted]

4.1.1. Group 1A Schedule

The 40 participants in Group 1A will have blood drawn at randomization (Day 1) for TNA testing, and TSH and autoantibody testing. These participants will receive both ciprofloxacin and AV7909 and undergo four ciprofloxacin PK sessions. They will have a final blood draw for TNA on Day 37 and will complete their final visit for safety including a blood draw for TSH and autoantibodies on Day 51. Note: testing of samples for TSH levels and autoantibodies will be performed only if medically indicated (ie, as per PI's discretion based on a report of a potential AESI).

Ciprofloxacin (500 mg by mouth [per os] every 12 hours [q 12 hr]) will be administered intermittently, ie, on Days 4-9, Days 22-24 and Days 31-37. Participants will use the same supply of ciprofloxacin in the clinic and for self-administration at home.

AV7909 (0.5 mL) will be administered by IM injection delivered on:

- Day 8 (Note: this will be administered in the evening following completion of the PK session and administration of the evening antibiotic)
- Day 23

Ciprofloxacin PK sessions will be performed on Days 4, 8, 31, and 35. On days with PK sessions, blood samples for measurement of ciprofloxacin concentrations will be 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 (± 5 min through hr 4, then ± 15 min thereafter). Ciprofloxacin pre-dose or trough values (all samples collected prior to the morning dose of ciprofloxacin) will be measured on Days, 4, 5, 6, 7 and 8; and again on Days 31, 32, 33, 34 and 35. The ciprofloxacin pre-dose values on Days 4, 8, 31 and 35 serve as the t=0 values for the PK sessions on those days as well as contributing to the two trough value analyses used to evaluate achievement of steady state before and after vaccination.

4.1.2. Group 1B Schedule

As shown in Figure 2 except for clinic visits for PK and trough value sampling, the 30 participants in Group 1B will receive otherwise identical treatment to those in Group 1A. They will have blood drawn at randomization (Day 1) for TNA, TSH and autoantibody testing and will receive a supply of ciprofloxacin after they have been randomized into Group 1. They will begin taking ciprofloxacin on Day 4, self-administering the antibiotic intermittently on Days 4-9, Days 22-24, and Days 31-37. Following randomization, they will have four scheduled clinic visits. The first two will be on Day 8 and Day 23, when they receive their first and second vaccinations with AV7909. Their third clinic visit will be on Day 37 when they will have a final blood draw for TNA and their fourth and final planned clinic visit will occur on Day 51 and includes a blood draw for TSH and autoantibodies.

4.1.3. Group 2A Schedule

The 40 participants in Group 2A will have blood drawn at randomization (Day 1) for TNA, TSH and autoantibody testing. These participants will receive both doxycycline and AV7909 and will undergo four PK sessions. They will have a blood draw for TNA on Day 37 and will complete their final visit for safety including a blood draw for TSH and autoantibodies on Day 51.

[redacted]

Doxycycline (100 mg by mouth [per os] every 12 hours [po q 12 hr]) will be administered intermittently ie, on Days 2-9, Days 22-24 and Days 32-38, in three courses, the exact format for which will be provided in the Pharmacy Manual. Participants will use the same supply of doxycycline in the clinic and for self-administration at home.

AV7909 (0.5 mL) will be administered by IM injection on:

- Day 8 (Note: this will be administered in the evening following completion of the PK session)
- Day 23

Doxycycline PK sessions will be performed on Days 2, 8, 32 and 38. On days with PK sessions, blood samples for measurement of doxycycline concentrations will be 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 (± 5 min through hr 4, then ± 15 min thereafter). Doxycycline pre-dose or trough values (all samples collected prior to the morning dose of doxycycline) will be measured on Days 2, 3, 4, 5, 6, 7 and 8; and again on Days 32, 33, 34, 35, 36, 37 and 38. The doxycycline pre-dose values on Days 2, 8, 32 and 38 serve as the t=0 values for the PK sessions on those days as well as contributing to the two trough analyses used to evaluate achievement of steady state before and after vaccination.

4.1.4. Group 2B Schedule

As shown in Figure 2 except for clinic visits for PK and trough value sampling, the 30 participants in Group 2B will receive otherwise identical treatment to those in Group 2A. They will have blood drawn at randomization (Day 1) for TNA, TSH and autoantibody testing and will receive a supply of doxycycline after they have been randomized into Group 2. They will begin taking doxycycline on Day 2, self-administering the antibiotic intermittently on Days 2-9, Days 22-24 and Days 32-38. Following randomization, they will have four scheduled clinic visits. The first two will be on Day 8 and Day 23, when they receive their first and second vaccinations with AV7909. Their third clinic visit will be on Day 37 when they will have a final blood draw for TNA and their fourth and final planned clinic visit will occur on Day 51 and includes a blood draw for TSH and autoantibodies.

4.1.5. Group 3 Schedule

The 70 participants in Group 3 will have blood drawn at randomization (Day 1) for TNA, TSH and autoantibody testing. They receive two doses of AV7909, the first on Day 8 and the second on Day 23. They will have a final blood draw for TNA on Day 37 and will complete their final visit for safety including a blood draw for TSH and autoantibodies on Day 51.

4.2. Scientific Rationale for Study Design

The study design is similar to that of an earlier trial (EBS.AVA.009: NCT01753115; Longstreth et al, 2018) conducted with the predecessor anthrax vaccine, BioThrax. As was done in that trial, antibiotic administration will be intermittent rather than continuous in order to reduce antibiotic exposure thereby presumably reducing the risks of adverse effects from these antibiotics in these healthy participants. In this trial, as in the previous trial, the aim is to characterize the single dose and steady state PK profiles of ciprofloxacin or doxycycline before and after vaccination to

[redacted]

determine whether vaccination affects antibiotic PK. Additionally, a second aim is to evaluate whether administration of either of these antibiotics affects the immunogenicity of AV7909 when evaluated with the TNA assay two weeks after the last vaccination of a 0-, 2-week schedule.

4.3. Justification of the Dose and Schedule

4.3.1. AV7909

The AV7909 formulation, dose, route of administration and dosing schedule being used in this study are the same as those being used in the licensure-enabling clinical trial being conducted concurrently (Study EBS.AVA.212). The formulation of 0.5 mL AVA and 0.25 mg CPG 7909, administered IM as two 0.5 mL doses, 2 weeks apart, was selected for further development based on the following observations in two previously conducted AV7909 clinical trials {Hopkins et al, 2013; Hopkins et al, 2016}.

- Keeping the AVA content at 0.5 mL (compared to 0.25 mL) maintained immunogenicity
- Increasing the CPG 7909 content beyond 0.25 mg to 0.5 mg increased the incidence and severity of both local and systemic reactions as assessed with a participant e-diary without enhancing immunogenicity
- Injection site reactogenicity was similar to that observed for BioThrax
- At 0.25 mg CPG 7909, a lower amount of unbound CPG could potentially reduce the risk of off-target immune activation

4.3.2. Ciprofloxacin

The ciprofloxacin dose (500 mg), dosing schedule [twice a day (q 12 hr)] and route of administration [by mouth (po)] being used in this study are those that would be used for PEP in the event of anthrax exposure and similar to those that were used in the prior PEP study conducted with ciprofloxacin and BioThrax {EPDG, 2014}. In this study and the prior BioThrax study (Study EBS.AVA.009), ciprofloxacin administration occurs on an intermittent daily rather than a continuous daily dosing schedule, with the assumption that intermittent dosing would achieve the required single dose and steady state concentrations needed prior to and following the vaccination schedule, as well as the immunogenicity endpoints while restricting the antibiotics administered to the minimum to achieve these ends.

Ciprofloxacin will be administered intermittently in three courses that will be used both by site staff for in-clinic visits and by participants when they are at home. The course format in terms of number of tablets and when participants will receive each course will be described in the Pharmacy Manual.

In addition to ensuring the achievement of steady state concentrations before and after the complete two-dose series of the vaccine, the selected ciprofloxacin dosing periods reflect the time when the inflammatory and immunosuppressive effects of ciprofloxacin are most likely to affect the antibody response to AV7909 {Takahashi et al, 2005; Kaminski et al, 2010}. The

[redacted]

intermittent dosing schedule was chosen in the hopes of minimizing any adverse effects from ciprofloxacin. This strategy appeared to have been successful in the BioThrax plus ciprofloxacin study in that ciprofloxacin-related AEs were low in number, frequently reported as related to both ciprofloxacin and BioThrax, generally mild in severity and resolved without sequelae by the end of the study {EPDG, 2014}.

4.3.3. Doxycycline

The doxycycline dose (100 mg), dosing schedule [twice a day (q 12 hr)] and route of administration [by mouth (po)] being used in this study are those that would be used for PEP in the event of inhalation exposure to anthrax. As with ciprofloxacin, doxycycline administration will occur on an intermittent daily rather than a continuous daily dosing schedule for the same reason this approach is used for ciprofloxacin. This schedule will provide the required single dose and steady state PK dosing regimens needed and, in addition to achieving the needed steady-state concentrations before and after vaccination, is designed to achieve the immunogenicity end-points while restricting the antibiotics administered to the minimum required to achieve these ends.

However, since the half-life of doxycycline is considerably longer than that of ciprofloxacin (15-16 hours after a single dose and 22 or more hours after multiple doses compared to 3-7 hours for ciprofloxacin), participants in Group 2 will receive a few more doses of antibiotic than those in Group 1. This is because we believe more days of dosing will be required to achieve steady state. Thus, Group 2 will receive seven days of dosing with doxycycline compared to five days used for ciprofloxacin before tests for steady state are applied.

Doxycycline will also be administered in three courses that will be used both by site staff for in-clinic visits and by participants when they are at home. The format of the courses in terms of number of tablets and when participants will receive each course will be described in the Pharmacy Manual.

The doxycycline dosing periods were chosen because they have been shown to have an effect on humoral immunity in mice {Woo et al, 1999} and to affect post-vaccination cell-mediated immunity in swine {Pomorska-Mól et al. 2014}, suggesting it could also affect the antibody response to AV7909. The intermittent dosing schedule was chosen in the hopes of minimizing any adverse effects from doxycycline.

4.4. End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of this study through the 12-month final safety follow-up phone contact (ie, Day 388 ± 14 d). Participants who do not complete the study are considered to have been withdrawn from the trial (refer to Section 7.3).

The End of Study Date is defined as the date of the last participant's final safety follow-up call, or earlier if the participant's last follow-up contact occurs before this time point.

[redacted]

5. STUDY POPULATION

Participants will be recruited at up to five clinical research centers in the United States. At least 210 healthy adults meeting the eligibility criteria will be randomized 1:1:1 to one of the three IP groups: 70 in Group 1 (AV7909 + ciprofloxacin), 70 in Group 2 (AV7909 + doxycycline) and 70 in Group 3 (AV7909 alone). Groups 1 and 2 will each have two subgroups; the A subgroup (N=40) will undergo PK sessions while the B subgroup (N = 30) will not. Approximately the first 40 participants who are randomized into Groups 1 and 2 will be assigned to Treatment Group 1A or Group 2A, while those who are randomized into Groups 1 and 2 thereafter will be assigned to Groups 1B or 2B.

No waivers of inclusion and/or exclusion criteria will be permitted in the trial. The sites will be asked to implement procedures that will ensure a representative racial distribution among recruited participants and result in populations that are gender- and age-balanced (ie, between 40-60% male with 40-60% of participants in the two age ranges of 18-30 years of age and 31-45 years of age).

5.1. Inclusion Criteria

Individuals must meet all of the following inclusion criteria for study participation:

1. Written informed consent obtained from the participant (dated, signed, and captured in the medical chart at the site).
2. A male or female, aged 18 to 45 years of age, inclusive, at the time of informed consent.
3. Healthy condition as established by medical history and clinical examination before entering into the study.
4. Have a body mass index (BMI) less than or equal to 35.0 kg/m^2 at the Screening visit.
5. Have adequate venous access for phlebotomies.
6. For a woman of childbearing potential (WOCBP), negative pregnancy test at Screening and pre-randomization on Day 1, not currently breastfeeding, and no intention to become pregnant during the study period through 12 months after last receipt of any investigational product (IP).

   Every female participant is considered to be a WOCBP unless she is surgically sterile (ie, has had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy) or postmenopausal [which is defined as >12 consecutive months without menses and a Screening FSH of >30 mIU/mL]. Adequate birth control (as defined here) must be initiated at least one month prior to randomization on Day 1 and used throughout the trial. Adequate birth control methods are sexual abstinence, intrauterine device/system (IUD/IUS), birth control pills, implantable or injectable contraceptives (eg, Norplant® or Depo-Provera®), removable birth control device (eg, NuvaRing® or Evra® patches) or double-barrier method of birth control (diaphragm in combination with contraceptive jelly or condoms in conjunction with contraceptive jelly, cream or foam), tubal ligation, or have a monogamous relationship with vasectomized partner who has been vasectomized for 6 months or more prior to the participant's trial entry.

[redacted]

Female participants randomized to Groups 1 or 2: be willing to add a double-barrier method, IUD, or abstinence as back-up forms of birth control since ciprofloxacin and doxycycline may decrease the effectiveness of birth control pills, implantable or injectable contraceptives.

5.2. Exclusion Criteria

Individuals meeting any of the following exclusion criteria will be excluded from study participation:

1. A Screening clinical laboratory test result greater than the central laboratory's upper limit of normal (ULN) for aspartate aminotransferase (AST), alanine aminotransferase (ALT), random glucose, total bilirubin, blood urea nitrogen (BUN), or creatinine. Other serum chemistry parameters that are not within the reference range will not be considered exclusionary unless deemed clinically significant by the principal investigator.
2. History of allergic reaction or intolerance to quinolone antimicrobials or any medical condition that would contraindicate the use of ciprofloxacin, including and not limited to vascular disorders, tendon disorders, certain genetic connective tissue disorders (eg, Marfan and Ehlers–Danlos syndrome), prolongation of QT interval, seizures, peripheral neuropathy, increased risk of *C. difficile* infection (see ciprofloxacin prescribing information in the Pharmacy Manual).
3. History of allergic reaction or intolerance to tetracycline antibiotics or any medical condition that would contraindicate the use of doxycycline including an increased risk of *C. difficile* infection, increases in BUN or an increased sensitivity to direct sunlight or ultraviolet radiation resulting in erythema (see doxycycline prescribing information in the Pharmacy Manual).
4. Has a need for any of the prohibited medications in Section 6.5.1 or requires the medications/foods within the prohibited times in Section 5.3.1.1.
5. Have a tattoo/scar/birthmark or any other skin condition affecting the deltoid area that may interfere with injection site assessments.
6. History of anthrax disease, suspected exposure to anthrax, or previous vaccination with any anthrax vaccine.
7. Have previously served in the military any time after 1990 or plan to enlist in the military any time from Screening through the final telephone contact.
8. Previous anaphylactic reaction, severe systemic response, or serious hypersensitivity to a prior immunization or a known allergy to synthetic ODNs, aluminum, formaldehyde, benzethonium chloride (phemerol).
9. Plan to have an elective surgery at any point during the study until after the final safety phone contact.
10. Have donated or plan to donate blood within one month prior to enrollment or at any point during the study until after the final safety phone contact.

[redacted]

11. Use of any investigational or non-registered product (drug, vaccine or biologic) within 30 days preceding the dose of study vaccine, or planned use during the study until after the final safety phone contact.
12. Planned administration of any commercially-available vaccine from one week prior to the first study vaccination through two weeks after the last vaccination.
13. Have experienced chronic dosing (defined as more than 14 days) with any immune-modifying drugs within six months of study enrollment. This includes oral, intramuscular, intra-articular, intravenous, or inhalation corticosteroids except in the case of inhaled or intranasal medications for seasonal allergies (see Table 3).
14. Receipt of immunoglobulins and/or any blood products within the three months preceding study enrollment or at any point during the study period until after the final safety visit on Day 51.
15. An abnormal electrocardiogram (ECG) at screening interpreted as 'Abnormal, Significant'. Inclusion of participants with 'Abnormal, Insignificant' ECGs will be based on the principal investigator's discretion.
16. Have an active malignancy or history of metastatic or hematologic malignancy.
17. Have a history of an autoimmune, inflammatory, vasculitic or rheumaticor rheumatic disease including but not limited to systemic lupus erythematosus, Guillain-Barré syndrome, myasthenia gravis, polymyalgia rheumatica, diabetes mellitus type I, rheumatoid arthritis or scleroderma.
18. A positive laboratory evidence of hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) HIV-1 or HIV-2 infection.
19. Positive result on urine drug screen, any evidence of ongoing drug abuse or dependence (including alcohol), or recent history (over the past five years) of treatment for alcohol or drug abuse.
20. Has an acute disease at the time of enrollment.

    Note that screening lab tests may be delayed to allow the resolution of a transient acute condition or the subject may be rescreened according to procedures under Section 5.4.
21. Any medical condition that, in the opinion of the investigator, could adversely impact the participant's involvement or the conduct of the study.
22. Have a significant chronic condition (see Sponsor's guidance on significant chronic conditions in Appendix C), eg, serious cardiovascular, pulmonary, hepatic, type II diabetes mellitus or renal disease that, in the opinion of the investigator, would render treatment unsafe or would interfere with trial evaluations or completion of the study.
23. An opinion of the investigator that it would be unwise to allow the participant to be randomized into the study.
24. Member or immediate family member of an investigator site team.

[redacted]

5.3. Lifestyle Restrictions

Participants in the two antibiotic groups will have certain lifestyle restrictions with which they will need to comply and that the site staff will need to remind them on an on-going basis. In addition, for Group 1A and 2A participants, meals served during PK sessions need to observe these same limitations. Details of these restrictions are provided below.

5.3.1. Meals and Dietary Restrictions

5.3.1.1. Precautions for Participants Taking Ciprofloxacin or Doxycycline

Participants in Groups 1 and 2 should be informed that these antibiotics may be taken with or without food, but antacids containing magnesium or aluminum and multivitamin/supplement preparations with calcium, zinc or other metals, eg, iron, should be taken at least two hours before or six hours after antibiotic administration. Furthermore, the same schedule should be used for the consumption of dairy products (like milk or yogurt) or calcium-fortified juices and the timing of antibiotic dosing since absorption of antibiotic may be significantly reduced by consumption of dairy products. However, these antibiotics may be taken with a meal that contains these products. In addition, participants in Group 2 should avoid taking bismuth subsalicylate (Pepto Bismol®) within 2-3 hours of their doxycycline dose.

Participants should also be asked to limit their consumption of caffeine to 400 mg/day (equivalent to about 4 cups of coffee).

5.3.1.2. Special Meals for Participants on Days with PK Sessions

On their PK session days [Days 4, 8, 31 and 35 for Group 1A (ciprofloxacin) and Days 2, 8, 32 and 38 for Group 2A (doxycycline)], participants are to be provided a non-dairy breakfast, 30 to 60 min prior to dosing. This is to be followed over the course of the day with a light lunch and a light dinner/snack.

5.3.2. Activity Restrictions

Participants should be asked to limit their time in the sun and to avoid the use of sunlamps and tanning beds. Ciprofloxacin and doxycycline increase the sensitivity of the skin to the ultraviolet radiation both from the sun and from artificial sources such as sunlamps and tanning beds. All such exposures while on these medications can result in severe sunburns, blisters or swelling of the skin.

Participants should be reminded to avoid sun exposure but if they must go out to avoid the high UV hours of 10 am to 2 pm, to wear sunscreen and protective gear (hats, sunglasses and protective clothes) when they do go outside. If they develop any of the signs or symptoms of sunburn while on antibiotic, participants must be instructed to notify the site staff.

Participants in Group 1should be advised against engaging in strenuous physical activity as this may independently increase the risk of tendon rupture from ciprofloxacin.

During each PK session, participants should remain in a seated or semi-recumbent position for 2 hours post-dose and then maintain a light activity level throughout the course of the day.

[redacted]

5.4. Screen Failures

A screen failure is a participant from whom informed consent is obtained and documented in writing, but who is not subsequently randomized to study treatment. Reasons for screen failure are to be recorded in the electronic case report forms (eCRFs).

All screening procedures must occur 2 to 28 days before the Day 1 study visit, at which time participants are allocated to a treatment group. During the initial Screening visit, the Principal Investigator (PI) or designee will confirm, by documentation of the evaluation, any transient acute condition that may affect the participant's Screening clinical laboratory results (which should meet the criteria specified in Exclusion criterion 1). The clinical laboratory assessment can be performed at the same visit or delayed, allowing time for resolution of the transient acute condition (eg, delayed screening until resolution of febrile illness, delayed urine occult blood in a menstruating woman). The clinical laboratory testing for Screening will not be performed more than twice (one initial and one repeat test for a total of two times). If the laboratory results are abnormal due to a processing or handling error, the test will be repeated without counting towards the not-to-exceed total of twice performed.

Participants who are screen failures are permitted to be rescreened one time (only) according to the PI's discretion. In the event that the participant is rescreened for trial participation, a new informed consent form (ICF) must be signed. For example, if there are any delays between Screening and enrollment that cause eligible participants to fall outside the Screening window, these participants may be re-consented and rescreened. Participants who complete the rescreening and are randomized in the study will not be considered screen failures.

[redacted]

6. TREATMENTS

6.1. Treatment Administration

6.1.1. AV7909 Description

AV7909 is a preformulated, sterile, milky-white suspension for IM injection consisting of the AVA drug substance (AVA) and CPG 7909 adjuvant. All participants will receive one dose of AV7909 0.5 mL IM, consisting of 0.5 mL AVA and 0.25 mg CPG 7909, on Day 8 and one dose IM on Day 23.

The AV7909 vaccine, manufactured by [redacted], will be supplied in 6 mL (nominal fill volume) clear borosilicate glass multi-dose vials with rubber stoppers and flip-top aluminum seals for storage. A single vial is filled with approximately 6.1 mL. For purposes of this trial, only a single dose (0.5 mL) will be used from each vial.

Each vial will be labeled with the name, main constituents and volume of study product; route of administration; manufacturer name; characterization as “sterile” product and “multi-dose vial”; storage conditions; manufacturing (fill) date and lot number; and appropriate federal caution statement for investigational use product.

6.1.2. Ciprofloxacin Description

Ciprofloxacin hydrochloride, USP, a fluoroquinolone, is a synthetic broad-spectrum antimicrobial agent for oral administration. It is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3 \bullet HCl \bullet H_2O$.

Ciprofloxacin will be provided as tablets of ciprofloxacin hydrochloride at strength of 500 mg ciprofloxacin equivalent. The manufacturer and exact formulation, ie, excipients, and format for the tablets will be specified in the Pharmacy Manual.

6.1.3. Doxycycline Description

Doxycycline hyclate, USP, is a broad-spectrum antibiotic synthetically derived from oxytetracycline. The chemical designation is 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate. Doxycycline is a light-yellow crystalline powder. The hyclate has a molecular weight 1025.9 with an empiric formula of $(C_{22}H_{24}N_2O_8 \bullet HCl)_2 \bullet C_2H_6O \bullet H_20$.

Doxycycline will be provided as tablets of doxycycline hyclate at strength of 100 mg doxycycline equivalent. The manufacturer and exact formulation, ie, excipients, and format for the tablets will be specified in the Pharmacy Manual.

[redacted]

6.1.4. Administration of AV7909

AV7909 will be administered to all participants in all groups as a 0.5 mL IM vaccination in alternate arms on Days 8 and 23. Vaccinations will be administered in the clinic by authorized personnel once AEs have been assessed, vitals have been taken and a symptom-directed PE conducted. Females who have not demonstrated an FSH level >30 mIU/mL must also pass a urine pregnancy test (see Section 8.3.2).

Participants in Groups 1A and 2A will receive their first vaccination after the 12-hour PK sample in the evening of Day 8, and their second vaccination on Day 23. Site personnel who administer the vaccine should be trained in the early recognition of symptoms of anaphylactic reactions, a rare but potentially serious reaction to parenteral injections.

Sites should be prepared to treat participants experiencing clinically significant dyspnea or hypotension, wheezing or generalized urticarial reactions. Appropriate medical therapy for anaphylaxis should be administered, if indicated, which should include IM or subcutaneous epinephrine 1:1000, and may include corticosteroids, diphenhydramine, bronchodilators, intravenous volume expansion, and/or oxygen. Participants will be evaluated and carefully monitored until complete resolution of any signs and symptoms, should they occur.

If a participant in Groups 1or 2 has a moderate or severe illness and/or an oral temperature greater than 100.4°F within three days before vaccination 1, or any condition that, in the opinion of the Investigator, would render vaccination unsafe or would interfere with evaluations, these participants will be withdrawn from the study and will be considered ineligible for rescreening. These participants will be instructed to cease taking antibiotics but to continue with their e-diary for an additional 7 days beyond the day they ceased taking antibiotics at which point they will be asked to return to the site and complete the EWV procedures. If the reason for not receiving vaccine is an AE/SAE/AESI, the participants will be followed until the event has resolved, stabilized or the participant has been referred to another physician. These participants, having not received any vaccine, will not be included in the long-term follow-up nor will they have additional blood samples taken for TNA, TSH or autoantibodies.

Any participant in Group 3 who has a moderate or severe illness and/or an oral temperature greater than 100.4°F within three days before vaccination 1, or any condition that, in the opinion of the Investigator, would render vaccination unsafe or that would interfere with evaluations may be re-screened and re-randomized with the event which precluded vaccination being added to that participant's medical history. If such an event were to occur within three days of vaccination 2, the vaccination must be delayed but should still occur within the 1-day study window. Participants unable to receive vaccination 2 within the allowed study visit window will remain in the study and be followed for safety.

6.1.5. Administration of Ciprofloxacin

Ciprofloxacin (500 mg po q 12 hr) will be administered only to participants in Group 1. A total of 31 ± 2 doses will be administered in three courses, the exact format for which will be presented in the Pharmacy Manual.

Group 1A participants will nominally receive 17 of their 31 ciprofloxacin doses in the clinic whereas Group 1B will nominally receive two of their 31 ciprofloxacin doses in the clinic. The

[redacted]

remaining doses will be taken at home. Doses should be taken at the same times ± 30 min each day. Doses administered in the clinic will be recorded by the staff with the date and time of administration in each participant's source documents and eCRF. Doses self-administered at home will be recorded by the participant with time of administration in their e-diary. Refer to Section 8.3.5.1 for additional details on the e-diary. If a participant misses a dose, they should be instructed to take the dose as soon as remembered, but no later than within 4 hours of its scheduled time. The participant should then wait until the next scheduled dose. The participant should not take two doses at the same time.

Exact details regarding the format in which the doses will be provided to the participants will be provided in the Pharmacy Manual.

Certain foods and over-the-counter products can interfere with the absorption of ciprofloxacin so prior to administration of doses in the clinic, site staff should ask each participant if they have eaten certain dairy products (such as milk or yogurt) or taken magnesium/aluminum antacids, other highly buffered drugs, or other products containing calcium, iron or zinc since their last dose and if so record this information along with the timing of intake, eg, 6 hours since their last dose. This information along with other precautions that need to be followed when taking ciprofloxacin will be provided to participants when they are given their supplies of ciprofloxacin for self-administration (see Section 5.3.1).

6.1.6. Administration of Doxycycline

Doxycycline (100 mg po q 12 hr) will be administered only to participants in Group 2. A total of 35 ± 2 doses will be administered in three courses as shown in Figure 2.

Group 2A participants will nominally receive 20 of their 35 doxycycline doses in the clinic whereas Group 2B will nominally receive two of their 35 doxycycline doses in the clinic. The remaining doses will be taken at home. Doses should be taken at the same times ± 30 min each day. Doses administered in the clinic will be recorded by the staff with the date and time of administration in each participant's source documents and eCRF. Doses self-administered at home will be recorded by the participant with the time of administration in their e-diary. Refer to Section 8.3.5.1 for additional details on the e-diary. If a participant misses a dose, they should be instructed to take the dose as soon as remembered, but no later than 4 hours of its scheduled time. The participant should then wait until the next scheduled dose. The participant should not take two doses at the same time.

Exact details regarding the format in which the doses will be provided to the participants will be provided in the Pharmacy Manual.

Certain foods and over-the-counter products can interfere with the absorption of doxycycline so prior to administration of doses in the clinic, site staff should ask each participant if they have eaten certain dairy products (such as milk or yogurt) or taken magnesium/aluminum antacids, other highly buffered drugs, or other products containing calcium, iron or zinc since their last dose and if so record this information along with the timing of intake (eg, 6 hours since their last dose). This information along with other precautions that need to be followed when taking doxycycline will be provided to participants when they are given their supplies of doxycycline for self-administration (see Section 5.3.1).

[redacted]

6.2. Acquisition/Preparation/Handling/Storage/Accountability

6.2.1. Acquisition

AV7909 liquid suspension for injection and oral antibiotics [ciprofloxacin and doxycycline (exact formats will be specified in the Pharmacy Manual)] will be shipped to investigational sites from the drug depot following institutional review board/independent ethics committee (IRB/IEC) and Emergent approval. All shipments will be accompanied by TempTale® temperature monitors to record any excursions outside of required storage conditions, ie, refrigerated storage [36 to 46ºF (2-8 ºC)] for the vaccine and room temperature [68° to 77°F (20-25 ºC)] for the antibiotics (ciprofloxacin or doxycycline). Detailed instructions for inventory receipt, temperature excursions, and IP resupply will be provided in the Pharmacy Manual.

6.2.2. Preparation of Investigational Product for Injection

Vaccine vials should be removed from the storage unit and allowed to sit at room temperature for approximately 15 minutes before administration. Vaccine doses should be drawn into a syringe only when administration is eminent. The stability of the vaccine stored in the syringes has not been determined. A site staff member, licensed to administer medication/vaccination, will prepare each dose of AV7909 into a syringe according to the following instructions:

- A separate 1- or 1½-inch 23- or 25-gauge sterile needle and separate 1.0 mL syringe will be used for each participant.
- Gently roll the vial of AV7909 between the hands to ensure that the suspension is homogeneous.
- Visually inspect the product for particulate matter and discoloration prior to preparing into the syringe. If the product appears discolored or has visible particulate matter, DO NOT USE the contents of the vial. THE VIAL SHOULD BE QUARANTINED and reported to the CRO according to the instructions in the Pharmacy Manual.
- Wipe the rubber stopper with an alcohol swab and allow to air dry before inserting the needle.
- Withdraw 0.5 mL of investigational product from the vial into a sterile syringe for administration. The volume and contents of the syringe will be verified by a second person before administration.
- Reseal the vial and cover it with tamper-evident tape to indicate no additional doses may be withdrawn from the vial.

AV7909 should not be mixed with any other product in the syringe.

6.2.3. Handling

Detailed instructions for packaging, labeling, and shipping as well as inventory receipt, and IP resupply will be provided in the Pharmacy Manual.

[redacted]

6.2.4. Product Storage and Stability

6.2.4.1. AV7909

Each shipment of AV7909 will arrive in a refrigerated carton containing vaccine and a TempTale™ temperature recorder that will be reviewed before use of the vaccine. Immediately upon receipt of each shipment of vaccine, vials are to be refrigerated at 36 to 46ºF (2 to 8ºC). AV7909 should not be frozen. Storage temperature must be continuously monitored and recorded. To guarantee proper storage conditions, the minimum, actual and maximum temperature in the storage refrigerator shall be continuously monitored for correct temperature. A back-up power source for the refrigerator is required. The study vaccine should be stored in a locked room, with access restricted to necessary site personnel.

6.2.4.2. Ciprofloxacin

Each shipment of ciprofloxacin will arrive in an insulated container with a temperature monitoring device which at a minimum displays the minimum and maximum temperature encountered while in transit. Ciprofloxacin is to be stored at room temperature [68° to 77°F (20° to 25°C)]. The ciprofloxacin should be stored with access restricted to necessary site personnel with temperature log for recording ambient temperature daily.

6.2.4.3. Doxycycline

Each shipment of doxycycline will arrive in an insulated container with a temperature monitoring device that at a minimum displays the minimum and maximum temperature encountered while in transit. Doxycycline is to be stored at room temperature [68° to 77°F (20° to 25°C)]. The doxycycline should be stored with access restricted to necessary site personnel with a temperature log for recording ambient temperature daily.

6.2.5. Investigational Product Experiencing Any Temperature Excursions

AV7909, ciprofloxacin or doxycycline which have been delivered/received at the site with temperature recorders indicating temperature excursions above or below their storage ranges will be immediately quarantined and not used by the site until the CRO study monitor has been informed and can determine an appropriate path forward. Similarly, if any IP is subjected to such temperature excursions while held at the site, the CRO study monitor must be contacted for further instructions.

6.2.6. Accountability

The Investigator will maintain complete records of receipt, storage and administration of investigational products at the investigator site. For the AV7909 vaccine, this will include lot number, the dose/volume administered, and the time, date, and site of administration. The latter information will be recorded in the participant's source documents along with the initials of the administering individual. NO VIALS OF VACCINE, including empty, damaged or partially used vials are to be destroyed or discarded during the conduct of the study. At the completion of the study, once all vaccine accountability is complete and queries resolved, the site will be responsible for discarding all remaining vials of IP per the instructions in the site Pharmacy

[redacted]

Manual. For ciprofloxacin and doxycycline, the Investigator will record number of tablets received, lot number(s), and the number of tablets dispensed. For those tablets administered on site, the site will also record the date and time of administration on the appropriate eCRF page. The latter information will be recorded in the participant's source documents along with the initials of the administering individual. For antibiotic tablets dispensed to participants, participants will record in an e-diary the time of self-administration of these antibiotics at home and the sites will check e-diary records regularly as well as collect the antibiotic supplies at each applicable in-clinic visit and do a tablet count to check compliance. At the completion of the treatment period, once all antibiotic dose accountability is complete and queries resolved, the site will be responsible for discarding all remaining antibiotic doses per the instructions in the Pharmacy Manual.

6.3. Measures to Minimize Bias

6.3.1. Method of Treatment Assignment

After the ICF has been signed and dated by the participant and PI/designee but before any screening procedures are performed, the participant will be assigned a unique subject identification (ID) number by the site. To maintain confidentiality, the subject ID will be used to identify the participant for data collected in eCRFs throughout the trial and for all clinical laboratory samples. The investigational site will retain a master list linking the subject ID with the name, date of birth, and contact information of the participant. The master list is to be retained by the site only and is not to be collected by Emergent or its agents.

If a participant is rescreened, a new subject ID will be assigned. To link records to the same participant, the participant's previous subject ID will be recorded in the eCRF along with the new subject ID.

At the Randomization visit (Day 1), after the PI has confirmed that the participant meets all the inclusion criteria and none of the exclusion criteria, a central randomization process will be used to assign each participant to one of the three open-label IP groups. The sites will be asked to the extent possible to execute a recruitment process that achieves a representative racial/ethnic distribution in populations that are reasonably gender- and age-balanced (ie, at least 40% male with 40% of participants in the two age ranges of 18-30 years of age and 31-45 years of age).

A randomization plan will be prepared and finalized prior to randomization of the first participant. The specific instructions for randomizing participants will be provided in the Pharmacy Manual.

If a participant signs and dates the ICF but is not randomized within the screening period window, that participant is considered a screen failure unless he or she signs a new ICF, is re-screened and is randomized within the allowable window (refer to Section 5.4).

6.3.2. Blinding

Not applicable; this is an open-label study.

[redacted]

6.4. Treatment Compliance

Each dose of AV7909 vaccine will be administered by site personnel at the investigator site. The date and time of the vaccine administration will be recorded in the participant's source documents and on the eCRFs.

The antibiotics, ciprofloxacin or doxycycline, will be administered in-clinic by staff and self-administered by participants at home. Each dose of ciprofloxacin or doxycycline administered by the site personnel will be recorded in the participant's source documents and the eCRF with the date and time of administration.

Each dose of ciprofloxacin or doxycycline self-administered at home will be recorded by the participant in the e-diary along with the date. The investigator site personnel will review the compliance data recorded in the e-diary on a routine basis and will call or talk to any participants who fail to record their antibiotic doses on two or more occasions. Repeated non-compliance may warrant discontinuation although such participants will be followed for safety.

If a participant misses a dose of antibiotic (ciprofloxacin or doxycycline) at home, the missed dose should be documented in the e-diary. Participants missing an at-home dose of antibiotic will remain in the study. Participants will be reminded that they have a 4-hour window within which to take a forgotten dose and that the time they record in the e-diary should be the time the dose is actually taken rather than the time it should be taken. They will also be reminded that a late dose should not reset the schedule, ie, that even if they take one dose late, their next dose should be taken on their original dosing schedule, and that they should continue to maintain 12 hours between doses thereafter and never take two doses at the same time. Thus, if a participant normally takes doses at 7 am and 7 pm but forgets to take the 7 am dose until 10 am, he or she should still take the second dose at 7 pm.

Participants will be asked to bring their antibiotic supplies with them to the clinic at each visit so that staff can confirm the remaining number of doses to document compliance. Site staff will collect any doses remaining once a course is complete and supply the next course when it is needed.

Additionally, for Groups 1A and 2A, compliance will also be tracked via the individual ciprofloxacin or doxycycline serum concentrations that will be recorded in the pre-dose and trough values, which are being collected to demonstrate achievement of the steady state concentrations of these antibiotics before and after vaccination with AV7909.

6.5. Concomitant Therapy

Prior and concomitant medication information (medications used 30 days prior to Screening or medications used since the last study visit) will be recorded in the eCRF at screening, randomization and at each study visit when applicable.

The medication name, dose, route, frequency, indication, and stop and start days/times for each new medication will be recorded. For the purposes of this trial, concomitant medications will be defined to include prescription drugs and biologics, over-the-counter drugs as well as herbal and nutritional supplements.

6.5.1. Prohibited Medications

Prohibited and restricted medications for this study fall into two categories: those that are restricted because of their effect on inflammation, immunity and vaccination and those known to interact with either ciprofloxacin or doxycycline.

6.5.1.1. Medications Prohibited Due to Effects on Inflammation or the Immune System

Prohibited and restricted medications for all participants include anti-inflammatory or antipyretic medications, topical antihistamine eye drops, nasal steroids, vaccines, immunosuppressive therapy, cytotoxic therapy and any experimental treatments (see Table 3).

Table 3: Medications Prohibited for all Participants

Category	Generic Name and Examples of Associated Brand Names
Anti-inflammatory or antipyretic medication: prohibited within 24 hours prior to or after vaccination	Glucocorticoids, aspirin-containing medication, NSAIDs, acetaminophen-containing medication Motrin, Advil®, Co-Advil®, Bayer®, Tylenol® Excedrin® Topical hydrocortisone **Note:** NSAIDs should be used (if medically indicated) with caution (outside 24 hours prior to or after vaccination) by participants in Group 1, because in pre-clinical studies and post-marketing the combination of high doses of quinolones with NSAIDs has been shown to provoke convulsions (see ciprofloxacin prescribing information in the Pharmacy Manual).
Aspirin withheld on each day of vaccination, but may be resumed the following day	Low-dose aspirin (≤ 81 mg/day)
Any commercially-available vaccine (except that for anthrax) through two weeks after the last vaccination	Including but not limited to vaccines for influenza, shingles, hepatitis B, pneumococcal, tetanus, yellow fever, pertussis, cholera, adenovirus, diphtheria, rabies virus haemophilus b, hepatitis A, human papillomavirus, measles, mumps, Japanese encephalitis virus, meningococcal vaccine, polio virus, plague, rotavirus, zoster vaccine, smallpox
Immunomodulatory agents through the final follow-up phone call. Note: inhalation use (eg, for seasonal allergies) is permitted.	Any systemic corticosteroids including, but not limited to, generic and brand names of: betamethasone, budesonide, cortisone acetate, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone.
Cytotoxic Therapy	Any of the alkylating agents, platinum coordinating complexes, antimetabolites or natural products used in current therapeutic regimens for cancer or rheumatic diseases including but not limited to generic and brand names of: methotrexate, cyclophosphamide, azathioprine, methotrexate, mercaptopurine, bendamustine, streptozocin, cisplatin, chlorambucil and hydroxyurea.

[redacted]

Category	Generic Name and Examples of Associated Brand Names
Investigational Medicinal Product	Product that is used in a clinical investigation.
Blood thinners and anti-coagulants (Groups 1A and 2A)	Any medication that might increase the risk of bleeding including but not limited to heparin and its derivatives, warfarin and other vitamin K antagonists, oral factor Ax inhibitors, any reversible or irreversible inhibitor of coagulation receptor $P2Y_{12}$, any glycoprotein IIa/IIIa antagonist, or any PAR-1 antagonist
Parenteral Immunoglobulins or Blood Products	Any of the approved intravenous (IV), subcutaneous (SC), or intramuscular (IM) human immune globulins (IG) or the human hyperimmune globulins (hhIG) or animal derived immune globulin (aIG) products including but not limited to: any IGIV, IGIM or IGSC; any anthrax hhIG, botulism hhIG, cytomegalovirus hhIG, hepatitis B hhIG, Rho(D) hIG, vaccinia hIG, or rabies hhIG; or any anti-thymocyte aIG, anti-scorpion venom aIG, anti-snake venom aIG, anti-spider venom aIG, anti-digoxin aIG, anti-botulinum toxin aIG, or anti-thymoglobulin aIG.

6.5.1.2. Medications Known to Interact with Ciprofloxacin

Prohibited and restricted medications for participants in Group 1 include those that are primarily metabolized by human cytochrome 450P1A2 (CYP1A2), but also those that are metabolized by CYP3A4 since ciprofloxacin is a strong inhibitor of CYP1A2 and a moderate inhibitor of CYP3A4, as well as products that can affect the absorption of ciprofloxacin such as antacids, multivitamins, or supplements that contain magnesium, aluminum, calcium, iron or zinc. If required, the latter medications should be taken 2 hours before or 6 hours after a ciprofloxacin dose. Refer to the ciprofloxacin prescribing information (in the Pharmacy Manual) where medications which are known to interact with ciprofloxacin are listed and should not be taken by participants in Group 1 of this study.

A more extensive list of medications is provided at the following URL: https://online.epocrates.com/drugs/50110/ciprofloxacin/Monograph {Athenahealth 2019a}. With the exception of those indicated to be contraceptives and those which may be components of antacids, multivitamins, or supplements that contain magnesium, aluminum, calcium, iron, or zinc, all medications, vaccines and supplements found at the above URL are also prohibited for participants in Group 1 of this study.

6.5.1.3. Medications Known to Interact with Doxycycline

Prohibited and restricted medications for participants in Group 2 can be found in the doxycycline prescribing information (provided in the Pharmacy Manual)**Error! Reference source not found.**. A more extensive list of medications is provided at the following URL: https://online.epocrates.com/drugs/20310/doxycycline/Monograph {Athenahealth 2019b}. With the exception of those indicated to be contraceptives and those which may be components of antacids, multivitamins, or supplements that contain magnesium, aluminum, calcium, iron, or zinc, all medications, vaccines and supplements found at the above URL are also prohibited for participants in Group 2 of this study.

[redacted]

7. STOPPING RULES, DISCONTINUATION/WITHDRAWAL CRITERIA AND PROCEDURES

7.1. Entire Study

Study enrollment and vaccinations may be temporarily halted by the DSMB or the Sponsor if any of the following occur, pending further evaluation:

- three or more dosed participants having the same Grade 3 or higher AE
- three suspected unexpected serious adverse reactions (SUSARs) within the same body system as assessed by the Sponsor
- five potential AESIs considered related to the IP, as assessed by the Sponsor
- a single DSMB-assessed AESI, considered to be related to the IP by the PI

These events will be reviewed by the DSMB and a recommendation will be made regarding vaccinations, continuation of study, or study termination. The procedures for DSMB notification and review of SUSARs, AESIs, and other significant events will be outlined in the DSMB Charter (refer to Section 8.5).

Emergent, BARDA, the IRB/IEC and/or FDA reserve the right to terminate the study at any time for clinical or administrative reasons. This study may be terminated due to safety concerns, failure to meet expected enrollment goals, administrative reasons or at Emergent's discretion. If the study is terminated prematurely, Emergent will provide written notification to all investigators and regulatory authorities and will specify the reason(s) for early termination. The investigator must inform the IRB/IEC promptly and provide the reason(s) for the termination.

7.2. Individual Site

The CRO will promptly notify Emergent if the trial is terminated by the PI or the IRB/IEC at the site.

Any particular site may be terminated from the trial at the discretion of the PI, Emergent, or IRB/IEC, eg, for non-enrollment of participants or non-compliance with the protocol. Emergent may decide to replace a terminated site.

7.3. Individual Participants

All participants have the right to withdraw at any point during treatment without prejudice. The PI can also discontinue a participant from a trial at any time if medically necessary or for reasons of noncompliance.

Every attempt will be made to follow participants for safety for the entire duration of the trial through the Month 12 safety follow-up providing they have received at least one vaccination. Participants in Groups 1 and 2 who discontinue treatment prematurely for any reason after receiving the first dose of antibiotic but prior to receipt of the first vaccination will be encouraged to return to the clinic for the Early Withdrawal procedures minus the blood draws for autoantibodies, TSH and TNA. Participants who discontinue treatment prematurely for any reason after receiving the first vaccination will be encouraged to continue in the study for any

[redacted]

remaining study visits (for safety assessments only) and the safety follow-up phone calls at Months 3, 6, 9 and 12 (post-vaccination).

If a participant discontinues treatment and/or involvement in the study, the reason(s) must be fully evaluated and recorded appropriately in source documents and eCRFs. Reason for discontinuation of treatment and reason for withdrawal from the study are to be recorded separately on eCRFs. If the participant is being discontinued because of an AE, that AE will be indicated as the reason for discontinuation and/or study withdrawal.

Randomized participants who withdraw for any reason will not be replaced in this trial.

7.3.1. Discontinuation of Study Treatment

Study treatment, either administration of antibiotic (ciprofloxacin or doxycycline) or vaccination with AV7909, will be permanently discontinued in any participants if they meet any of the individual participant halting rules described in Table 4. The date when the event occurred or was detected and the specific reason, ie, which criterion was met, for discontinuation of treatment, is to be recorded on the eCRF.

Table 4: Criteria for Discontinuation of Treatment in Individual Participants

No.	Item
1.	Participants experiencing any of the AEs described in the WARNINGS AND PRECAUTIONS sections of the ciprofloxacin and doxycycline package inserts (provided in the Pharmacy Manual) will be discontinued. In the case of ciprofloxacin, these include, but are not limited to, tendinitis and tendon rupture, hypersensitivity reactions (including rash and jaundice), peripheral neuropathy, central nervous system effects, exacerbation of myasthenia gravis, hepatotoxicity, *Clostridium difficile*-associated diarrhea, prolongation of the QT interval, and a variety of other serious adverse reactions including severe dermatologic reactions, eg, toxic epidermal necrolysis, Stevens-Johnson syndrome; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities and inflammatory responses, eg, interstitial nephritis; acute renal insufficiency or failure; allergic pneumonitis; hepatitis; jaundice; acute hepatic necrosis or failure. In the case of doxycycline, these include, but are not limited to, *Clostridium difficile*-associated diarrhea, photosensitivity manifesting as an exaggerated sunburn reaction; super infection and overgrowth of non-susceptible organisms including fungi; severe skin reactions, such as exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS); intracranial hypertension (IH, pseudotumor cerebri) manifesting as headache, blurred vision, diplopia, and vision loss has been observed with papilledema detectable on fundoscopy; delayed skeletal development in the fetuses of pregnant women [tetracyclines/ however, data for doxycycline are limited]. NB: Pregnancy would require discontinuation from the trial (refer to Section 9.4).
2.	Grade 2 or greater hypersensitivity, ie, anaphylaxis, allergic reaction (such as, but not limited to difficulty breathing, rapid increase in heart rate, dizziness, nausea, evidence of rash, or periorbital swelling) believed by the PI to be associated with receipt of any of the IPs

[redacted]

No.	Item
3.	Any Grade 3 or higher systemic reactogenicity symptom assessed by e-diary and confirmed by the PI
4.	Any AE that would pose a risk to the participant as determined by the PI if continued administration of IP were to occur.
5.	Any violation of eligibility criteria discovered after randomization that would pose a risk to the participant, as determined by the PI and agreed to by the Medical Monitor (MM)
6.	Febrile illness (fever > 100.4 °F) within three days prior to either vaccination (Exception: For the second vaccination, the visit may be rescheduled to another day outside this three-day period providing it will not fall outside the required visit window for vaccination two [Section 8.1].)
7.	Receipt of AV7909 associated with loss of cold chain
8.	Suspected or confirmed pregnancy (refer to Section 9.4). (Exception: In the case of suspected pregnancy, if the subsequent serum pregnancy test is negative, the antibiotic dosing may be resumed and the vaccination visit (second vaccination only) may be rescheduled to another day providing it does not fall outside the required visit window for the visit [Refer to Section 8.1].)
9.	Scheduling or other conflict results in the second vaccination visit falling outside the required window
10.	Receipt of prohibited medication (see Section 6.5.1) as determined by the PI and agreed by the MM
11.	Causally-related Grade 3 or higher unsolicited AE as assessed by the PI[a]
12.	Causally-related SAE or potential AESI as assessed by the Sponsor

AE=adverse event; AESI = adverse event of special interest; IP=investigational product; MM = medical monitor; PI=principal investigator, SAE = serious adverse event,
[a]Any AE is considered to be related to the vaccine administration if assessed by the PI as being "possibly" or "probably" or "definitely" related.

All participants who have received at least one vaccination will be encouraged to continue with the scheduled study safety evaluations, including any remaining study visits (safety assessments only), collection of samples for TSH and autoantibodies (only if medically indicated) and the safety follow-up calls. Participants who decline will be encouraged to complete the EWV (see Section 8.1.8) and followed for safety through the 12-Month (Day 388 ± 14d) Safety Follow-up phone call. If the discontinuation was due to an AE, participants will be followed until the event has resolved or stabilized or the participant has been referred to an outside physician.

7.3.2. Withdrawal from the Study

A participant may withdraw from the study at any time, for any reason. The PI may withdraw a participant from the study for the following reasons:

[redacted]

1. Occurrence of an AE that in the opinion of the PI, warrants the participant's permanent discontinuation from treatment (if having received at least one vaccination, the participant will be encouraged to continue in the study for safety follow-up only).
2. Death.
3. Lost to follow-up.
4. Non-compliance with IP.
5. Physician decision.
6. Withdrawal of consent by participant.
7. Study terminated by Sponsor.
8. Other (eg, if Sponsor requests withdrawal of a participant, ceases dosing due to unacceptable toxicity).

If the PI determines a participant has been noncompliant with study procedures, the PI will document the reason for noncompliance, and the participant will be withdrawn from the study. Reason(s) for study withdrawal will be recorded on the End of Study eCRF page. Participants who withdraw from the study treatment will be asked to continue with the scheduled study safety evaluations, including any remaining study visits (safety assessments only), collection of samples for autoantibodies and the safety follow-up calls details of which are provided in Section 8.1.6.3, Section 8.1.6.4, and Section 8.1.7. Participants who decline will be encouraged to complete the EWV. The EWV procedures are discussed in Section 8.1.8.

7.4. Lost to Follow-up

Participants who cannot be contacted during the in-clinic evaluation period through the Day 51 (Final In-clinic Visit) or at the final 12-month (388 ± 14 d) safety follow-up phone contacts and who do not have a known reason for study withdrawal (eg, withdrew consent or AE) will be classified as "lost to follow-up" as the reason for study discontinuation in the eCRFs. The site will make three attempts to contact the participant by telephone. In the event the site is unable to reach the participant by telephone, the site will attempt to contact the participant via certified mail or an alternative similar method where appropriate. The time-period between contact attempts will be greater than one week apart.

[redacted]

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Schedule of Assessments

Involvement for the individual participant in this study from first visit to last visit inclusive of the screening visit and the safety follow-up phone calls will be approximately 14.5 months. Screening will occur within approximately one month (Day -28 to Day -2) of study start. Eligible participants will be randomized into one of the three groups shown in Table 2. All participants undergo the same assessments and procedures during screening and immediately following randomization; however, thereafter each group has its own schedule of assessments. The following sections provide detailed lists of assessments to be performed by visit, first starting with a section on the Screening and Randomization visits which are common to all participants and then followed with sections for each of the five groups.

8.1.1. Screening, Randomization/Enrollment and Initial Blood Draws for TNA and Autoantibodies

8.1.1.1. Screening (Days -28 to -2)

Participants will be screened for participation in the trial from 2 to 28 days prior to the Day 1 (randomization) visit. The Screening period begins once the participant signs and dates the ICF. The following activities will occur during the Screening visit or period:

1. Ensure review and completion of all required information on the ICF and capture in site source documentation and eCRF.
2. Assign subject ID number.
3. Record demographics.
4. Record complete medical history including current signs and symptoms which will be recorded as AEs only if they result from a study-related procedure(s).
5. (For WOCBP only) document in the participant's chart about counsel received for the requirements around type and timing of an adequate method of contraception, including the participant's preferred method.
6. Perform complete physical examination including an ECG.
7. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature), height and weight and determine BMI.
8. Record medications taken in last 30 days.
9. Collect blood and urine samples for clinical laboratory tests (see Section 8.3.2)
    a. Depending on a woman's fertility status conduct a serum pregnancy test (for WOCBP) or an FSH test (for postmenopausal women). Any female participant whose FSH test returns a value ≤30 mIU/mL will need to take a serum pregnancy test.
    b. Hematology.
    c. Serum chemistry.

[redacted]

d. Viral serology (human immunodeficiency virus [HIV] antibodies, hepatitis B surface antigen [HBsAg], and hepatitis C antibody).
e. Urinalysis.
f. Urine drug screen.

10. Review for study eligibility against inclusion/exclusion criteria.

8.1.1.2. Randomization/Enrollment and Initial Blood Draws for TNA and Autoantibodies: Day 1

Day 1: Morning

The following will occur on Day 1 prior to randomization:

1. Update medical history including signs and symptoms, which will be recorded as AEs only if the event results from a study-related procedure.
2. Assess vital signs.
3. Conduct symptom-directed PE.
5. Record medications taken since screening visit.
6. Confirm continued use of an adequate method of contraception and collect urine sample for pregnancy test for WOCBP (if positive, the participant must not be randomized; upon receipt of a confirmatory negative serum pregnant test result, the participant may be rescheduled for the Day 1 visit, providing the visit falls within the required window of the screening procedures).
7. Review for study eligibility against inclusion/exclusion criteria, to include a review of all safety and screening laboratory test results and status of ongoing AEs since the prior visit.

After the PI has confirmed that the participant meets all the inclusion criteria and none of the exclusion criteria, the participant will be randomized into one of the three IP groups.

1. Randomize eligible participants.
2. For participants who are WOCBP and randomized to Group 1 or 2: Re-educate participants that ciprofloxacin and doxycycline may decrease the effectiveness of birth control pills, implantable or injectable contraceptives. Instruct the participant to add a double-barrier method, IUD, or abstinence as back-up forms of birth control.
3. All randomized participants will have blood samples taken for TNA, TSH and autoantibodies.
4. Participants randomized to Group 2A will be instructed to return the same evening so that they can enter the first doxycycline PK session the following morning (See Section 8.1.4).
5. Participants randomized to Group 1A will be instructed to return to the site the evening of Day 3 so that they can enter the first ciprofloxacin PK session on Day 4 (See Section 8.1.2).

[redacted]

6. Participants randomized to Group 1B or 2B will be:
   - provided their antibiotics [ciprofloxacin (Group 1B) or doxycycline (Group 2B)],
   - provided instructions on the dosing regimen (twice daily at 12-hour intervals), beginning on the following day (Day 2) for those taking doxycycline (Group 2B) and beginning on Day 4 for those taking ciprofloxacin (Group 1B).
   - informed about the dietary and lifestyle precautions required when taking each antibiotic (see Section 5.3).
   - introduced to the e-diary for antibiotic compliance (see Section 8.3.5.1) and give instructions on how the e-diary should be used to record self-administered antibiotic doses.
   - instructed to return on Day 8 to receive their first vaccination (See Sections 8.1.3 and Section 8.1.5).

   Any participant who does not have or who does not wish to use their own personal device to access the e-diary will at this time be supplied a hand-held device by the site.
7. Participants randomized to Group 3 will be instructed to return on Day 8 to receive their first vaccination (Section 8.1.6).

8.1.2. Group 1A: Ciprofloxacin + AV7909 with Ciprofloxacin PK Sessions

Shown in Table 5 is a schedule of events for Group 1A participants from screening until the end of the study. Following the table are detailed descriptions of the daily activities that the sites are expected to conduct for each of the column headings identified in the table. Note that this detail starts with PM Admit (Evening Admission) as the detailed activities during Screening and Group Assign (Randomization) were covered previously in Section 8.1.1.

Table 5 Schedule of Events for Group 1A: Ciprofloxacin + AV7909 with Ciprofloxacin PK

	Screening	Group Assign	PM[a] Admit	PK[b]	AM[a] Visits	Vac	At Home†	TNA	Final Visit	Safety Calls	EWV USV‡
Study Day(s)	**-28 to -2**	**1**	**3, 7, 30, 34**	**4, 8, 31, 35**	**5-7 32-34**	**8 23***	**9, 22, 24, 36, 37**	**37**	**51**	**114, 205, 296, 388**	**NA**
Visit Window	**NA**		**§TBD**	**NA**	**NA**	**± 1 d***		**± 1 d**	**± 1 d**	**± 14 d**	
Sign, date ICF & assign ID	X										
Review eligibility[c]	X	X	X			X					
Medical history & demographics	X	X									
Physical examination[d]	X								X		X
ECG[e]	X										
Vital signs[f]	X	X		X		X			X		X
Pregnancy test[g]	X	X	X (D3&D7 only)			X			X		X
FSH test[g]	X										

[redacted]

	Screening	Group Assign	PM[a] Admit	PK[b]	AM[a] Visits	Vac	At Home†	TNA	Final Visit	Safety Calls	EWV USV‡
Study Day(s)	**-28 to -2**	**1**	**3, 7, 30, 34**	**4, 8, 31, 35**	**5-7 32-34**	**8 23***	**9, 22, 24, 36, 37**	**37**	**51**	**114, 205, 296, 388**	**NA**
Visit Window	**NA**		**§TBD**	**NA**	**NA**	**± 1 d***		**± 1 d**	**± 1 d**	**± 14 d**	
Collect sample for hematology[h]	X								X		X
Collect sample for serum chemistry[i]	X								X		X
Collect sample for urinalysis[j]	X								X		X
Urine drug screen[k]	X										
HIVAb/HBsAg/HCVAb	X										
Concomitant medications[l]	X	X	X	X	X	X	X	X	X	X	X
Randomize eligible participants		X									
Symptom-directed PE[m]		X				X			X		X
Blood draws for TNA[n]		X						X			
Cipro dosing & compliance[o,p]			X	X	X	X	X	X			X [p]
Cipro pre-dose or trough				X	X						
Cipro PK[q]				X							
AV7909 vaccination[r]						X					
Participant e-diary + tools[s]		X		X	X	X	X	X	X		X
Staff review of e-diaries[t]			X[s]	X	X	X	X	X	X		X
AEs[u], SAEs, AESIs[v]	X	X	X	X		X			X	X	X
Collect TSH & autoantibody samples[w]		X							X		X [w]

For the abbreviations used above please refer to Table 1 of the protocol. *The ± 1 d window applies only to the second vaccination on Day 23 (note: the second course of antibiotic treatment will have to shift accordingly) and needs discussion with CRO. †At Home Days are only those days where both doses of ciprofloxacin are taken at home. § The TBD window only applies to Day 30 and can at best be +1 d but needs discussion with sites and CRO because it will require a 1 day forward shift for all activities thereafter until Day 37 which may not need to shift because of its window. ‡For EWV occurring within the visit window of Day 37, a blood sample for TNA will be drawn.

[a] PM and AM admissions must be timed so that ciprofloxacin can be administered in the clinic within a 12 hr ± 30 min window of the prior AM or PM dose.

[b] For each PK session, the sites will manage the meals and activity of participants as detailed in Protocol Section 5.3.1 and Protocol Section 5.3.2.

[c] Eligibility will be reviewed before each vaccination, either the evening before (ie, on Day 7) or the morning of vaccination (ie, on Day 23).

[d] Physical examinations (PE) will be conducted as described in Protocol Section 8.3.3.

[e] Electrocardiograms (ECGs) will be conducted and interpreted at screening as described in Section 8.3.3.

[f] Vital signs will be administered as described in Protocol Section 8.3.4.

[g] Pregnancy tests (serum and/or urine) will be administered to all WOCBP as described in Protocol Section 8.3.2. Serum pregnancy test will be performed at Screening visit for WOCBP, while urine pregnancy tests for WOCBP required before each vaccination will be administered either the evening before (ie, on Day 7) or the morning (ie, on Day 23) of vaccination. Note: for WOCBP in group 1A, UPT is required at Day 3 and Day 7 only (during overnight stay visit); it is not required at Day 30 or 34. FSH test will be performed at Screenining visit only for postmenopausal women.

[h] Hematology tests will be conducted as described in Protocol Section 8.3.2.

[i] Serum chemistry tests will be conducted as described Protocol Section 8.3.2.

[j] Urinalyses will be conducted as described in Protocol Section 8.3.2.

[k] Urine drug screens will be conducted as described in Protocol Section 8.3.2.

[l] Concomitant medications will be identified and recorded along with their indication as described in Protocol Section 6.5.

[m] Symptom-directed PEs will be conducted as described in Protocol Section 8.3.3.

[redacted]

[n] Blood samples for TNA assessment on Day 1 will be collected in the morning following randomization. Those on Day 37 will be collected after the final dose of ciprofloxacin has been administered. A TNA sample will also be collected if EWV occurs within the visit window of Day 37 as described in Protocol Section 8.1.8.
[o] Ciprofloxacin doses (500 mg po q 12 hr) will be administered as described in Protocol Section 6.1.5 with the first dose being administered on Day 4 when the cipro PK group enters their first PK session.
[p] Ciprofloxacin dose compliance will be managed as described in Protocol Section 6.4.
[q] Blood samples for assessment of ciprofloxacin concentrations will be collected as detailed in Protocol Section 8.4.
[r] Vaccinations with AV7909 will be administered as described in Protocol Section 6.1.4.
[s] All Participants will be provided with an e-diary for post vaccination follow up along with a thermometer and an injection site reaction measurement tool. Participants in Group 1 and 2 will be provided with an e-dairy for antibiotic compliance. All participants will be trained on the use of these tools and the e-diaries as described in Protocol Section 8.3.5.1.
[t] Staff will begin reviewing the e-diaries on Day 6 and will review them at regular intervals thereafter.
[u] AEs will be collected at all clinic visits through Day 51/EWV as described in detail in Protocol Section 9.
[v] AEs, SAEs and potential AESIs will be collected during the Safety Follow-up Telephone Calls (see Protocol Section 8.1.7).
[w] Serum samples for TSH & autoantibody testing will be collected from all participants and tested as described in Protocol Section 8.3.2 (ie, at Day 1, Day 51, and at EWV if the subject received at least one vaccination). Additional samples for TSH & autoantibody testing may be requested (eg, based on participant report(s) of a potential AESI); blood draws for additional TSH and/or autoantibody testing should be performed as part of an unscheduled visit.

8.1.2.1. Group 1A: Day 3 – Overnight Stay # 1

1. Admit to the clinic for overnight stay #1.
2. Review and record AE assessments and changes in medications in participant's medical history unless they are related to study procedures in which case they are recorded as AEs.
3. For WOCBP, collect urine and perform a UPT. Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who have received at least one dose of any IP and where conception occurs prior to 12 months after last receipt of that IP will be followed to outcome.

8.1.2.2. Group 1A: Day 4 – Pre-vaccine Single Dose Ciprofloxacin PK Session

1. Provide a non-dairy breakfast 30 to 60 min prior to dosing; provide a light lunch and a light dinner/snack over the course of the day.
2. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
3. Collect blood sample for ciprofloxacin t=0 concentration determination prior to administration of AM dose of ciprofloxacin.
4. Administer AM ciprofloxacin dose following blood sample collection for t=0 antibiotic concentration determination and record time of administration in the source document and eCRF; ensure the participant remains semi-recumbent for two hours after dosing and continues with a light activity level throughout the day.
5. Blood samples for ciprofloxacin PK assessment are to be collected at the following time points: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post-dose (± 5 min through hr, 4 then ± 15 min thereafter). The exact time of sample collection is to be recorded in the source document and eCRF.

[redacted]

6. Administer ciprofloxacin dose (500 mg po) in the clinic after the final 12-hour ciprofloxacin PK sample has been collected and 12 hours after morning dose (± 30 min), record exact time of administration in the source document and eCRF.
7. Record anyAEs reported.
8. Conduct a symptom-directed PE (if required).
9. Prior to being discharged from the clinic, participants will be:
    - informed about the dietary and lifestyle precautions required when taking ciprofloxacin (see Section 5.3)
    - Review the e-diary instructions on how the e-diary should be used to record compliance for the antibiotic doses (see Section 8.3.5.1 e-diary).

    Any participant who does not have or who does not wish to use their own personal device to access the e-diary will at this time be supplied a hand-held device by the site;

8.1.2.3. Group 1A: Days 5, 6 and 7 – Morning

1. Review e-diary, confirm compliance with ciprofloxacin dosing (Days 6 and 7), and ask if there were any associated changes in concomitant medications.
2. Collect blood samples for determination of ciprofloxacin trough concentrations prior to administering the AM dose of ciprofloxacin on Days 5, 6 and 7; record times of administration of ciprofloxacin in source document and eCRF.
3. Prior to discharge from the clinic on Day 5, participants will
    - receive a ciprofloxacin supply to take with them
    - be reminded to take their evening dose of ciprofloxacin approximately 12 hours (± 30 min) from the time their morning dose was provided and to bring their supply of ciprofloxacin with them when they return the following morning.
    - be reminded of the dietary and activity precautions associated with the use of ciprofloxacin (see Section 5.3).
4. On Days 5 and 6, the evening dose (q 12 hr) of ciprofloxacin is to be self-administered at home (at about the same times [± 30 min] each day). The participant will to be instructed/reminded to record the date and time of administration of ciprofloxacin in the e-diary
5. On the mornings of Days 5, 6 and 7, staff will review the e-diary entries with the participant, confirm compliance with ciprofloxacin dosing (Days 5 and 6), review and record any changes in concomitant medications, and will remind participants on Days 5 and 6 to return the next morning for another clinic visit.
6. At the end of each clinic visit, participants will be reminded to take their evening dose of ciprofloxacin and to be aware of the dietary and activity precautions associated with the use of ciprofloxacin (see Section 5.3).

[redacted]

7. Prior to discharge on morning of Day 7, participants will be reminded to return to clinic that evening for the second overnight admission.

8.1.2.4. Group 1A: Day 7 – Evening & Overnight Stay # 2

1. Admit to clinic for overnight stay #2.
2. For WOCBP, collect urine and perform a UPT. Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who have received at least one dose of any IP and where conception occurs prior to 12 months after last receipt of that IP will be followed to outcome.
3. Staff will review ciprofloxacin supply with participant, checking the remaining content against the dosing records in the e-diary to document compliance and using this supply to provide the evening ciprofloxacin dose which is to be administered 12 hours (± 30 min) after morning dose; record time of administration of ciprofloxacin in source document and the eCRF.

8.1.2.5. Group 1A: Day 8 – Pre-vaccine Steady-State Ciprofloxacin PK Session & Vaccination #1

1. Provide a non-dairy breakfast 30 to 60 min prior to dosing; provide a light lunch and a light dinner/snack over the course of the day.
2. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
3. Review eligibility for vaccination.
4. Review and record AEs.
5. Reassess concomitant medications.
6. Perform symptom-directed PE, if required.
7. Collect blood sample for ciprofloxacin t=0 concentration determination prior to administration of AM dose of ciprofloxacin.
8. Administer AM dose of ciprofloxacin following blood sample collection for t=0 antibiotic concentration determination and record time of administration in the source document and the eCRF; ensure the participant remains semi-recumbent for two hours after dosing and continues with a light activity level throughout the day.
9. Blood samples for ciprofloxacin PK assessment are to be collected at the following time points: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post-dose (± 5 min through hr 4, then ± 15 min thereafter).
10. Administer ciprofloxacin 500 mg po in the clinic after the final 12-hour ciprofloxacin PK sample has been collected and 12 hours after morning dose (± 30 min).
11. Administer AV7909 vaccination #1 after the 12 hr blood sample for ciprofloxacin PK has been collected and after the PM dose of ciprofloxacin has been administered. Participants

[redacted]

will be monitored for at least 30 minutes following vaccine administration for any adverse effects especially anaphylaxis.

12. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature) at 30 ± 5 minutes post-vaccination.
13. At some point during the day but prior to being discharged from the clinic, the participant's ciprofloxacin supply will be reviewed, checking the remaining content against the dosing records.
14. Prior to discharge from the clinic, the participant will be provided and trained on an e-diary to capture local and systemic reactogenicity events (ie, reactogenicity e-diary) and to record daily for at least seven days following each vaccination. If a reaction is not resolved at seven days postvaccination, the participant is to continue completing the e-diary daily until they are symptom free for two consecutive days. Participants will be provided with an injection site reaction measurement tool and shown how to use it to measure the size of certain reactogenicity events associated with vaccination, rate the intensity and where to enter this information in the e-diary (see Section 8.3.5.1).
15. When the participants are discharged from the clinic, they will be reminded:
    - about the diet and activity precautions that must be followed when taking ciprofloxacin (see Section 5.3).
    - to continue to use the antibiotic e-diary to record the times they take their ciprofloxacin doses each day, and to use their reactogenicity e-diary to record any vaccination reactions, if applicable.

8.1.2.6. Group 1A: Days 9, 22 and 24 (At home)

On Days 9, 22 and 24, the participant is to self-administer ciprofloxacin (500 mg po q 12 hr) at home [at about the same times (± 30 min) each day]. The participant will continue with the e-diary as described in Section 8.3.5.1.

It is required that participants self-administer ciprofloxacin on the day before (morning and evening, the day of (evening), and the day after vaccination (morning and evening). The site must contact the participant to remind them to begin their second course of the antibiotics (ie, the site should contact the pariticpant within 24 hours of the anticipated start day for the second course of antibiotics in relation to the scheduled second vaccination date).Any participant who needs to shift the day they come for their second vaccination must be reminded by the site to start their ciprofloxacin dosing on the appropriate day, eg, if the second vaccination shifts to Day 22, then the participant will need to be reminded to start taking ciprofloxacin on the morning and evening of Day 21 in order to meet the dosing requirement.

8.1.2.7. Group 1A: Day 23 (± 1d) – Vaccination # 2

1. Review e-diary entries with the participant, recording of ciprofloxacin dosing, reminding the participant of the precautions in Section 5.3.
2. Review and record AEs, including any ongoing since the prior visit.

[redacted]

3. Reassess concomitant medications.
4. Perform symptom-directed PE, if required.
5. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
6. For WOCBP, collect urine and perform a UPT (prior to AV7909 vaccination). Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who receive at least one dose of any IP and where conception occurs prior to 12 months after last receipt of any IP will be followed to outcome.
7. Review eligibility for continuing vaccination.
8. Administer AM ciprofloxacin dose; record time of administration in source document and the eCRF.
9. Administer AV7909 vaccination #2; this should occur after ciprofloxacin dosing. Participants should be monitored for at least 30 minutes following vaccine administration for any adverse effects especially anaphylaxis.
10. Assess vital signs at 30 ± 5 min post-vaccination (seated/semi-recumbent blood pressure, heart rate, respiratory rate, and temperature).
11. After vaccination, participants will be reminded to continue to use the e-diary and injection site reaction measurement tool to capture the adverse events associated with vaccination, and to record the dates and times they take their self-administered ciprofloxacin doses. (See Section 8.3.5.1 e-diary).
12. Prior to discharge on Day 23 ± 1d, participants will be reminded to continue to take their ciprofloxacin on the following day (Day 24) and to return to clinic in seven days for the third overnight admission.

8.1.2.8. Group 1A: Day 30 – Evening & Overnight Stay # 3

1. Admit to the clinic for overnight stay #3.
2. Staff will review e-diary entries with participant, discussing the use of concomitant medication as well as any vaccination reactions.
3. Staff will review ciprofloxacin supply from participant, cross-referencing the content against the dosing records in the e-diary to document compliance.

8.1.2.9. Group 1A: Day 31 – Post-vaccine Single Dose Ciprofloxacin PK Session

1. Provide a non-dairy breakfast 30 to 60 min prior to dosing; provide a light lunch and a light dinner/snack over the course of the day.
2. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
3. Collect blood sample for ciprofloxacin t=0 concentration determination prior to administration of AM dose of ciprofloxacin.

[redacted]

4. Administer AM dose of ciprofloxacin following blood sample collection for t=0 concentration determination and record time of administration in the source document and the eCRF; ensure the participant remains semi-recumbent for two hours after dosing and continues with a light activity level throughout the day.
5. Blood samples for ciprofloxacin PK assessment are to be collected at the following time points: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post-dose (± 5 min through hr 4, then ± 15 min thereafter).
6. Administer ciprofloxacin 500 mg po in the clinic after the final 12-hour ciprofloxacin PK sample has been collected and 12 hours after morning dose (± 30 min).
7. Following the PK session, staff will review any changes in concomitant medications.
8. When the participants are discharged from the clinic, they will be reminded:
    - about the diet and activity precautions that must be followed when taking ciprofloxacin (see Section 5.3).
    - to continue to use the antibiotic e-diary to record their ciprofloxacin doses each day, and to use the reactogenicity e-diary to record any vaccination reactions, if applicable, see Section 8.3.5.1 (Participant e-diary).

8.1.2.10. Group 1A: Days 32, 33 and 34 – Morning

1. Review e-diary, confirm compliance with ciprofloxacin dosing to document compliance, discuss any changes in concomitant medications, as well as any vaccination reactions if still ongoing and remind participants about the dietary and activity precautions that must be followed when taking ciprofloxacin (see Section 5.3).
2. Collect blood samples for determination of ciprofloxacin trough concentrations prior to the in-clinic administration of the AM dose of ciprofloxacin on Days 32, 33 and 34; record times of administration of ciprofloxacin in source document and the eCRF.
3. On Days 32 and 33, the evening dose (q 12 hr) of ciprofloxacin is to be self-administered at home (at about the same times [± 30 min] each day).
4. Prior to discharge on the morning of Day 34, participants will be reminded to return to clinic that evening for the fourth overnight admission.

8.1.2.11. Group 1A: Day 34 – Evening & Overnight Stay # 4

1. Admit to clinic for overnight stay #4.
2. Staff will review the participant's ciprofloxacin supply and review e-diary entries, conducting a compliance check of the remaining doses compared to the e-diary record. Staff will also ask if the participant required the use of concomitant medication as well as any vaccination reactions if still ongoing.
3. Administer ciprofloxacin 500 mg po 12 hours after morning dose (± 30 min).

[redacted]

8.1.2.12. Group 1A: Day 35: – Post-vaccine Steady-State Ciprofloxacin PK Session

1. Provide a non-dairy breakfast 30 to 60 min prior to dosing; provide a light lunch and a light dinner/snack over the course of the day.
2. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
3. Collect blood sample for ciprofloxacin t=0 concentration determination prior to administration of AM dose of ciprofloxacin.
4. Administer AM dose of ciprofloxacin (500 mg po) following blood sample collection for t=0 concentration determination and record time of administration in the source document and the eCRF; ensure the participant remains semi-recumbent for two hours after dosing and continues with a light activity level throughout the day.
5. Blood samples for ciprofloxacin PK assessment are to be collected at the following time points: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post-dose (± 5 min through hr 4, then ± 15 min thereafter).
6. Administer ciprofloxacin 500 mg po in the clinic after the final 12-hour ciprofloxacin PK sample has been collected and 12 hours after the morning dose (± 30 min).
7. Record concomitant medications.
8. Return ciprofloxacin supply to participant
9. When the participants are discharged from the clinic, they will be reminded:
    - about the diet and activity precautions that must be followed when taking ciprofloxacin (see Section 5.3).
    - to continue to use the antibiotic e-diary to record the times they take their ciprofloxacin doses each day and to use the reactogenicity e-diary to record any vaccination reactions, if applicable, see Section 8.3.5.1 (Participant e-diary).

8.1.2.13. Group 1A: Day 36 (At home)

Two ciprofloxacin doses (500 mg po morning and evening, q 12 hr) are to be self-administered at home on Day 36. The participant will continue with the e-diary as described in Section 8.3.5.1.

8.1.2.14. Group 1A: Day 37 (± 1d) – Blood Draw for TNA

The Day 37 visit to draw blood for immunogenicity may shift by ± 1 d. If such a shift in visit day occurs, the participant must remain on ciprofloxacin 500 mg po every 12 hours until the morning of that visit. In the event of such a shift, the participant's required number of doses of ciprofloxacin will vary. The Pharmacy Manual will contain a table detailing the dosing options for the final course of ciprofloxacin given a one-day shift from Day 37.

1. Participants will report to the clinic having taken their morning dose of ciprofloxacin at home.

[redacted]

2. Review participant's ciprofloxacin supply; count the number of remaining doses and compare to the e-diary record to document compliance; record total remaining in source document and eCRF.
3. Review other e-diary entries with participant. Discuss any changes in the use of concomitant medication as well as any vaccination reactions if still ongoing. Remind participants that they should still use sunscreen and avoid excessive sun exposure and strenuous sports until the Day 51 Final Study Visit.
4. Record concomitant medications.
5. Collect blood sample for TNA assessment.

8.1.2.15. Group 1A: Day 51 (± 1d) – Final In-Clinic Study Visit

1. Perform complete PE.
2. Review e-diary entries with participant and collect hand-held device if study provided.
3. Review and record AEs.
4. Record concomitant medications.
5. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
6. For WOCBP, collect and perform a UPT. Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who receive at least one dose of AV7909 or ciprofloxacin and where conception occurs prior to 12 months after last receipt of either IP will be followed to outcome.
7. Collect blood samples for hematology and serum chemistry.
8. Collect blood samples for TSH & autoantibodies.
9. Collect urine sample for urinalysis.

8.1.3. Group 1B: Ciprofloxacin + AV7909 without Ciprofloxacin PK

Shown in Table 6 is a schedule of events for Group 1B participants from screening until the end of the study. Following the table are detailed descriptions of the activities that the sites are expected to conduct for each of the column headings identified in the table once each participant has received his or her group assignment. Note that this detail starts following randomization for Group 1B which is when they receive their first course of ciprofloxacin although the actual activities for the trial do not begin until Day 4 when participants self-administer their first dose

[redacted]

of ciprofloxacin. The detailed activities during Screening and Group Assign (Randomization) were covered previously in Section 8.1.1.

Table 6: Schedule of Events for Group 1B: Ciprofloxacin + AV7909 without Ciprofloxacin PK

	Screening	Group Assign	At Home†	Vac	At Home†	TNA	Final Visit	Safety Calls	EWV USV‡
Study Day(s)	**-28 to -2**	**1**	**4-7**	**8 23***	**9, 22, 24, 31-37**	**37**	**51**	**114, 205, 296, 388**	**NA**
Visit Window	**NA**	**NA**		***± 1 d**		**± 1 d**	**± 1 d**	**± 14 d**	
Sign, date ICF & assign ID	X								
Review eligibility [a]	X	X		X					
Medical history & demographics	X	X							
Physical examination[b]	X						X		X
ECG[c]	X								
Vital signs[d]	X	X		X			X		X
Pregnancy test[e]	X	X		X			X		X
FSH test[e]	X								
Collect sample for hematology[f]	X						X		X
Collect sample for serum chemistry[g]	X						X		X
Collect sample for urinalysis[h]	X						X		X
Urine drug screen[i]	X								
HIVAb/HBsAg/HCVAb	X								
Concomitant medications[j]	X	X		X		X	X	X	X
Randomize eligible participants		X							
Symptom-directed PE[k]		X		X					
Blood draws for TNA[l]		X				X			
Cipro dosing & compliance[m,,n]		X	X	X	X	X			X[n]
AV7909 vaccination[o]				X					
Participant e-diary + tools[p]		X	X	X	X	X	X		X
Staff review of e-diaries[q]			X	X	X	X	X		X
AEs[r], SAEs & AESIs[s]	X	X		X			X	X	X
Collect TSH & autoantibody samples[t]		X					X		X

For the abbreviations used above please refer to Table 1 of the protocol. *The ± 1 d window applies only to the second vaccination on Day 23 (note: the second course of antibiotic treatment will have to shift accordingly). †At Home Days are only those days where both doses of ciprofloxacin are taken at home. ‡For EWV occurring within the visit window of Day 37, a blood sample for TNA will be drawn.

[a] Eligibility will be reviewed before each vaccination, ie, on Day 8 and Day 23.

[b] Physical examinations (PE) will be conducted as described in Protocol Section 8.3.3.

[c] ECGs will be conducted and interpreted at screening as described in Protocol Section 8.3.3.

[d] Vital signs will be administered as described in Protocol Section 8.3.4.

[e] Pregnancy tests (serum and/or urine) will be administered to all WOCBP as described in Protocol Section 8.3.2. Serum pregnancy test will be performed at Screening visit for WOCBP, while urine pregnancy tests for WOCBP will be required before each vaccination. At Screening visit only, FSH test will be performed for postmenopausal women.

[f] Hematology will be conducted as described in Protocol Section 8.3.2.

[redacted]

[g] Serum chemistry will be conducted as described Protocol Section 8.3.2.
[h] Urinalysis will be conducted as described in Protocol Section 8.3.2.
[i] Urine drug screens will be conducted as described in Protocol Section 8.3.2.
[j] Concomitant medications will be identified and recorded as described in Protocol Section 6.5.
[k] Symptom-directed PEs will be conducted as described in Protocol Section 8.3.3.
[l] Blood samples for TNA assessment on Day 1 will be collected in the morning following randomization. Those on Day 37 will be collected after the final dose of ciprofloxacin has been administered. A TNA sample will also be collected if EWV occurs within the visit window of Day 37 as described in Protocol Section 8.1.8.
[m] Participants receive their first course of ciprofloxacin following randomization. Format of the doses and distribution of subsequent courses will be described in the Pharmacy manual. Self-administration of ciprofloxacin starts on Day 4. Ciprofloxacin dose compliance will be managed as described in Protocol Section 6.4.
[n] Ciprofloxacin doses (500 mg po q 12 hr) will be administered as described in Protocol Section 6.1.2.
[o] Vaccinations with AV7909 will be administered as described Protocol Section 6.1.4.
[p] All participants will be provided with an e-diary for post vaccination follow up along with a thermometer and an injection site reaction measurement tool. Participants in Group 1 and 2 will be provided with an e-dairy for antibiotic compliance. All participants will be trained on the use of these tools and the e-diaries as described in Protocol Section 8.3.5.1.
[q] Staff will begin reviewing the e-diaries on Day 5 and will review them at regular intervals thereafter.
[r] AEs will be collected at all clinic visits through Day 51/EWV as described in detail in Protocol Section 9.
[s] AEs, SAEs and potential AESIs will be collected during the Safety Follow-Up Telephone Calls (see Protocol Section 8.1.7).
[t] Serum samples for TSH & autoantibody testing will be collected from all participants and tested as described in Protocol Section 8.3.2 (ie, at Day 1, Day 51, and at EWV if the subject received at least one vaccination). Additional samples for TSH & autoantibody testing may be requested (ie, based on the participant's report(s) of a potential AESI); blood draws for additional TSH and/or autoantibody testing should be performed as part of an unscheduled visit.

8.1.3.1. Group 1B: Days 4 to 7 (At home)

1. On Days 4 to 7, the participant will self-administer ciprofloxacin 500 mg po every 12 hours at home at about the same times (± 30 min) each day.
2. Participant will use the antibiotic e-diary to record the date and time of administration of ciprofloxacin.

8.1.3.2. Group 1B: Day 8 – Vaccination #1

1. Review eligibility.
2. Staff will review the ciprofloxacin supply and review the e-diary entries, conducting a compliance check of the remaining doses compared to the e-diary record. Staff will record ciprofloxacin doses to document compliance. Staff will also discuss any changes in the use of concomitant medication while reminding the participant of the precautions in Section 5.3.
3. Review and record AEs.
4. Conduct a symptom-directed PE, if required.
5. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
6. For WOCBP, collect and perform UPT (prior to AV7909 vaccination). Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who receive at least one dose of AV7909 or ciprofloxacin and where conception occurs prior to 12 months after last receipt of either IP will be followed to outcome.

[redacted]

7. Administer ciprofloxacin 500 mg po in AM prior to vaccination; the evening dose of ciprofloxacin 500 mg po will be self-administered at home 12 hours after the AM dose [and at approximately the same time (± 30 min) each day].
8. Administer AV7909 vaccination #1. Participants should be monitored for at least 30 minutes following vaccine administration for any adverse effects especially anaphylaxis.
9. Assess vital signs at 30 ± 5 min postvaccination.
10. Prior to being discharged from the clinic, the participant will be given and trained on an e-diary to capture local and systemic reactogenicity events (ie, reactogenicity e-diary) and to record daily for at least seven days following each vaccination. If a reaction is not resolved at seven days postvaccination, the participant is to continue completing the e-diary daily until they are symptom free for two consecutive days. Participants will be given aninjection site reaction measurement tool and shown how to use it to measure the size and assess the severity of certain reactogenicity events associated with vaccination. See Section 8.3.5.1 (e-diary) and remind participants about the diet and activity precautions that must be followed when taking ciprofloxacin (see Section 5.3).

8.1.3.3. Group 1B:Days 9, 22 and 24 (At home)

On Days 9, 22 and 24, the participant is to self-administer ciprofloxacin (500 mg po q 12 hr) at home [at about the same times (± 30 min) each day]. The participant will continue with the e-diary as described in Section 8.3.5.1.

It is required that participants self-administer ciprofloxacin on the day before (morning and evening), the day of (evening), and the day after (morning and evening) vaccination. The site must contact the participant to remind them to begin their second course of the antibiotics (ie, the site should contact the pariticpant within 24 hours of the anticipated start day for the second course of antibiotics in relation to the scheduled second vaccination date). Any participant who schedules vaccination 2 (on Day 23) to shift within the allowable window (± 1 d) will be reminded to start their ciprofloxacin dosing on the appropriate day, eg, if the second vaccination shifts to Day 22 then the participant will be reminded to start taking ciprofloxacin on the morning and evening of Day 21 in order to meet the dosing requirement.

8.1.3.4. Group 1B: Day 23 (± 1 d) – Vaccination #2

1. Staff will review ciprofloxacin supply and review against e-diary entries conducting a compliance check of the remaining doses compared to the e-diary record. Staff will record ciprofloxacin doses to document compliance. Staff will discuss changes in the use of concomitant medication as well as any vaccination reactions if still ongoing while reminding the participant of the precautions in Section 5.3.
2. Review and record AEs.
3. Perform symptom-directed PE, if required.
4. Record concomitant medications.
5. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate, and temperature).

[redacted]

6. Review eligibility for continuing vaccination.
7. For female participants not exempted due to a screening FSH >30 mIU/mL, collect and perform UPT (prior to AV7909 vaccination). Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who receive at least one dose of any IP and where conception occurs prior to 12 months after last receipt of any IP will be followed to outcome.
8. Administer ciprofloxacin 500 mg po in AM; the evening dose will be self-administered at home.
9. Administer AV7909 vaccination #2; this should occur after ciprofloxacin dosing. Participants should be monitored for at least 30 minutes following vaccine administration for any adverse effects especially anaphylaxis.
10. Following the 30 (± 5) minutes of observation, repeat vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate, and temperature) measurement.
11. After e-diary review, participants will be reminded to continue to use the reactogenicity e-diary and injection site reaction measurement tool to capture the adverse events associated with vaccination, and to record the dates and times they self-administer their ciprofloxacin doses in the antibiotic e-diary. See Section 8.3.5.1 (e-diary).
12. Prior to discharge on Day 23, participants will be reminded to return to clinic in two weeks (± 1 d) on Day 37 ± 1 d for the final blood draws for TNA. Again, participants are to continue dosing with ciprofloxacin through the evening of Day 24 and discontinue dosing until Day 31. Their ciprofloxacin supply will be returned to them before they are discharged from the clinic.

8.1.3.5. Group 1B: Days 31 to 36 (At home)

On Days 31 to 37, the participant is to self-administer ciprofloxacin 500 mg po every 12 hours at home [at about the same times (± 30 min) each day]. The participant will continue with the e-diary as described in Section 8.3.5.1. The site must contact the participant to remind them to start their third course of ciprofloxacin within 24 hours of Day 31.

8.1.3.6. Group 1B: Day 37 (± 1 d) – Blood Draw for TNA

The Day 37 Visit may shift by ± 1 d. If such a shift occurs, the participant must remain on ciprofloxacin 500 mg po every 12 hours until the morning before the blood draw. In the event of such a shift, the participant's required number of doses of ciprofloxacin will vary. The Pharmacy Manual will contain a table detailing the dosing options for the final course of ciprofloxacin given a one-day shift from Day 37.

1. Participants will report to the clinic having taken their morning dose of ciprofloxacin at home.
2. Review participant's ciprofloxacin supply; count the number of remaining doses and compare to the e-diary record to document compliance; record total remaining in source document.

[redacted]

3. Review other e-diary entries with participant. Discuss any changes in the use of concomitant medication as well as any vaccination reactions if still ongoing. Remind participants that they should still use sunscreens and avoid excessive sun exposure and strenuous sports until the Day 51 Final Study Visit.
4. Record concomitant medications.
5. Collect blood sample for TNA assessment

8.1.3.7. Group 1B: Day 51 (± 1 d) – Final In-Clinic Study Visit

1. Perform complete PE.
2. Review e-diary entries with participant and collect hand-held device if study provided.
3. Review and record AEs.
4. Record concomitant medications.
5. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
6. For WOCBP, collect and perform UPT. Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who receive at least one dose of AV7909 or ciprofloxacin and where conception occurs prior to 12 months after last receipt of either IP will be followed to outcome.
7. Collect blood sample for hematology.
8. Collect blood sample for serum chemistry.
9. Collect blood sample for TSH and autantibodies.
10. Collect urine sample for urinalysis.

8.1.4. Group 2A: Doxycycline + AV7909 with Doxycycline PK Sessions

Shown in Table 7 is a schedule of events for Group 2A participants from screening until the end of the study. Following the table are detailed descriptions of the activities that the sites are expected to conduct for each of the column headings identified in the Table. Note that this detail starts with PM Admit (Evening Admission) as the detailed activities during Screening and Group Assign (Randomization) were covered previously in Section 8.1.1.

Table 7: Schedule of Events for Group 2A: Doxycycline + AV7909 with Doxycycline PK

	Screening	Group Assign	PM[a] Admit	PK[b]	AM[a] Visits	Vac	At Home†	TNA	Final Visit	Safety Calls	EWV USV‡
Study Day(s)	**-28 to -2**	**1**	**1[r], 7[c,e], 31, 37**	**2[r], 8, 32, 38**	**3-7 33-37**	**8 23[e]***	**9, 22, 24,**	**37**	**51**	**114, 205, 296, 388**	**NA**
Visit Window ±	**NA**		**[§]+ 1 d**	**NA**		***± 1 d**			**± 1 d**	**± 14 d**	
Read, sign, date ICF & receive ID	X										
Review eligibility	X	X	X			X[c]					

[redacted]

	Screening	Group Assign	PM[a] Admit	PK[b]	AM[a] Visits	Vac	At Home†	TNA	Final Visit	Safety Calls	EWV USV‡
Study Day(s)	**-28 to -2**	**1**	**1[r], 7[c,e], 31, 37**	**2[r], 8, 32, 38**	**3-7 33-37**	**8 23[e]***	**9, 22, 24,**	**37**	**51**	**114, 205, 296, 388**	**NA**
Visit Window ±	**NA**		**§+ 1 d**	**NA**		***± 1 d**			**± 1 d**	**± 14 d**	
Medical history & demographics	X	X									
Physical examination[d]	X								X		X
ECG[e]	X										
Vital signs[f]	X	X		X		X			X		X
Pregnancy test[g]	X	X	X (D7 only)			X			X		X
FSH test[g]	X										
Collect sample for hematology[h]	X								X		X
Collect sample for serum chemistry[i]	X								X		X
Collect sample for urinalysis[j]	X								X		X
Urine drug screen[k]	X										
HIVAb/HBsAg/HCVAb	X										
Concomitant medications[j]	X	X	X	X	X	X	X	X	X	X	X
Randomize eligible participants		X									
Symptom-directed PE[m]		X				X			X		
Blood draws for TNA[n]		X						X			
Doxy dosing & compliance[o,p]			X	X	X	X	X	X			X
Doxy pre-dose or trough				X	X						
Doxy PK[q]				X							
AV7909 vaccination[r]						X					
Participant e-diary + tools[x]		X		X	X	X	X	X	X		X
Staff review of e-diaries[t]			X	X	X	X	X	X	X		X
AEs[u], SAEs, AESIs[v]	X	X	X	X		X			X	X	X
Collect TSH & autoantibody samples[w]		X							X		X

For the abbreviations used above please refer to Table 1 of the protocol. *The ± 1 d window applies only to the second vaccination on Day 23 (note: the second course of antibiotic treatment will have to shift accordingly). †At Home Days are only those days where both doses of doxycycline are taken at home. § The +1 d window only applies to Day 31. ‡For EWV occurring within the visit window of Day 37, a blood sample for TNA will be drawn.

[a] PM and AM admissions must be timed so that doxycycline can be administered in the clinic within a 12 hr ± 30 min window of the prior AM or PM dose.

[b] For each PK session, the sites will manage the meals and activity of participants as detailed in Protocol Section 5.3.1 and Protocol Section 5.3.2.

[c] Eligibility will be reviewed before each vaccination, either the evening before (ie, on Day 7) or the morning of vaccination (ie, on Day 23).

[d] Physical examinations (PE) will be conducted as described in Protocol Section 8.3.3.

[e] ECGs will be conducted and interpreted at screening as described in Protocol Section 8.3.3.

[f] Vital signs will be administered as described in Protocol Section 8.3.4.

[g] Pregnancy tests (serum and/or urine) will be administered to all WOCBP as described in Protocol Section 8.3.2. Serum pregnancy test will be performed at Screening visit for WOCBP, while urine pregnancy tests for WOCBP required before each vaccination will be performed either the evening before (ie, on Day 7) or the morning of vaccination (ie, on Day 23). Note: for WOCBP in group 2A, UPT is required only at Day 7 (at the evening admission); it is not required at evening admissions at Day 1, 31 or 37. FSH test will be performed at Screenining visit only for postmenopausal women.

[redacted]

[h] Hematology tests will be conducted as described in Protocol Section 8.3.2.
[i] Serum chemistry tests will be conducted as described Protocol Section 8.3.2.
[j] Urinalysis will be conducted as described in Protocol Section 8.3.2.
[k] Urine drug screens will be conducted as described in Protocol Section 8.3.2.
[l] Concomitant medications will be identified and recorded as described in Protocol Section 6.5.
[m] Symptom-directed PEs will be conducted as described in Protocol Section 8.3.3.
[n] Blood samples for TNA assessment on Day 1 will be collected in the morning following randomization. Those on Day 37 will be collected after the morning dose of doxycycline has been administered. A TNA sample will also be collected if the EWV occurs within the visit window of Day 37 as described in Protocol Section 8.1.8.
[n] Symptom-directed PEs will be conducted as described in Protocol Section 8.3.3.
[o] Doxycycline dose compliance will be managed as described in Protocol Section 6.4.
[p] Doxycycline doses (100 mg po q 12 hr) will be administered as described in Protocol Section 6.1.6.
[q] Blood samples for assessment of doxycycline concentrations will be collected as detailed in Protocol Section 8.4.
[r] Vaccinations with AV7909 will be administered as described Protocol Section 6.1.4.
[s] All participants will be provided with an e-diary for post vaccination follow up along with a thermometer and an injection site reaction measurement tool. Participants in Group 1 and 2 will be provided with an e-dairy for antibiotic compliance. All participants will be trained on the use of these tools and the e-diaries as described in Protocol Section 8.3.5.1.
[t] Staff will begin reviewing the e-diaries on Day 3 and will review them at routine intervals thereafter.
[u] AEs will be collected at all clinic visits through Day 51/EWV as described in detail in Protocol Section 9.
[v] AEs, SAEs and potential AESIs will be collected during the Safety Follow-Up Telephone Calls (see Protocol Section 8.1.7).
[w] Serum samples for TSH & autoantibody testing will be collected from all participants and tested as described in Protocol Section 8.3.2 (ie, at Day 1, Day 51, and at EWV if the subject received at least one vaccination). Additional TSH & autoantibody testing may be requested (ie, based on the participant's report(s) of a potential AESI); additional TSH and/or autoantibody testing should be performed as part of an unscheduled visit.

8.1.4.1. Group 2A: Day 1 – Overnight Stay # 1

1. Admit to the clinic for overnight stay #1.
2. Review eligibility.
3. Review and record AE assessments and changes in concomitant medications in participant's medical history unless they are related to study procedures in which case they are recorded as AEs.

8.1.4.2. Group 2A: Day 2 – Pre-vaccine Single Dose Doxycycline PK Session

1. Provide a non-dairy breakfast 30 to 60 min prior to dosing; provide a light lunch and a light dinner/snack over the course of the day.
2. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
3. Collect blood sample for doxycycline t=0 concentration determination prior to administration of AM dose of doxycycline.
4. Administer AM dose of doxycycline following blood sample collection for t=0 antibiotic concentration determination and record time of administration in the source document and the eCRF; ensure the participant remains semi-recumbent for two hours after dosing and continues with a light activity level throughout the day.
5. Blood samples for doxycycline PK assessment are to be collected at the following time points: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post-dose (± 5 min through hr 4, then ± 15 min thereafter). The exact time of sample collection is to be recorded in the source document and eCRF.

[redacted]

6. Administer doxycycline dose (100 mg po) in the clinic after the final 12-hour doxycycline PK sample has been collected and 12 hours after morning dose (± 30 min), record exact time of administration in the source document and the eCRF.
7. Record any AEs reported.
8. Conduct a symptom-directed PE in response to any AEs reported.
9. Prior to being discharged from the clinic, participants will:
   - Be informed about the dietary and lifestyle precautions required when taking doxycycline (see Section 5.3).
   - Review the instructions on the use of the antibiotic e-diary to record compliance for the antibiotic doses (see Section 8.3.5.1 e-diary).

   Any participant who does not have or who does not wish to use their own personal device to access the e-diary will at this time be supplied a hand-held device by the site.

8.1.4.3. Group 2A: Days 3, 4, 5, 6 and 7 – Morning

1. Review e-diary, confirm compliance with doxycycline dosing (Days 6 and 7) and ask if there were any associated changes in concomitant medications.
2. Collect blood samples for determination of doxycycline trough concentrations prior to administering the AM dose of doxycycline on Days 3, 4, 5, 6 and 7; record times of administration of doxycycline in the source documents and eCRF.
3. Prior to discharge from the clinic on Day 3, participants will receive their first course of doxycycline and will be introduced to the dietary and activity precautions associated with the use of doxycycline (see Section 5.3).
4. On Days 3, 4, 5 and 6, the evening dose (q 12 hr) of doxycycline is to be self-administered at home [at about the same time (± 30 min) each day]. The participant will to be instructed/reminded to record the date and time of administration of doxycycline in the e-diary.
5. On the mornings of Days 4, 5, 6 and 7, staff will review the e-diary entries with the participant and confirm compliance with doxycycline dosing (Days 3, 4, 5 and 6).
6. At the end of each clinic visit, participants will be reminded to take their evening dose of doxycycline and to be aware of the dietary and activity precautions associated with the use of doxycycline (see Section 5.3).
7. Prior to discharge on morning of Day 7, participants will be reminded to return to clinic that evening for the second overnight admission and to bring their doxycycline supply with them.

8.1.4.4. Group 2A: Day 7 – Evening & Overnight Stay # 2

1. Admit to clinic for overnight stay #2.
2. Review eligibility for vaccination.

[redacted]

3. Staff will review the e-diary entries with participant, confirming antibiotic dosing compliance. Staff will then record AEs and any changes in concomitant medications.
4. For WOCBP, collect urine and perform a UPT. Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who have received at least one dose of any IP and where conception occurs prior to 12 months after last receipt of that IP will be followed to outcome.
5. Administer doxycycline 12 hours after morning dose (± 30 min); record time of administration of doxycycline in source document and in eCRF

8.1.4.5. Group 2A: Day 8 – Pre-vaccine Steady-State Doxycycline PK Session & Vaccination #1

1. Provide a non-dairy breakfast 30 to 60 min prior to dosing; provide a light lunch and a light dinner/snack over the course of the day.
2. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
3. Review and record AEs.
4. Reassess concomitant medications.
5. Perform symptom-directed PE, if required.
6. Collect blood sample for doxycycline t=0 concentration determination prior to administration of AM dose of doxycycline.
7. Administer AM dose of doxycycline following blood sample collection for t=0 antibiotic concentration determination; ensure the participant remains semi-recumbent for two hours after dosing and continues with a light activity level throughout the day.
8. Blood samples for doxycycline PK assessment are to be collected at the following time points: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post-dose (± 5 min through hr 4, then ± 15 min thereafter).
9. Administer doxycycline 100 mg po in the clinic after the final 12-hour doxycycline PK sample has been collected and 12 hours after morning dose (± 30 min).
10. Administer AV7909 vaccination #1 after the 12 hr blood sample for doxycycline PK has been collected and after the PM dose of doxycycline has been administered. Participants should be monitored for at least 30 minutes following vaccine administration for any adverse effects especially anaphylaxis.
11. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature) at 30 ± 5 minutes post-vaccination.
12. At some point during the day but prior to being discharged from the clinic, the participants' doxycycline supply will be returned to them.
13. Prior to discharge from the clinic, the participants will be given and trained on the e-diary to capture local and systemic reactogenicity events and to record daily for at least seven days following each vaccination. If a reaction is not resolved at seven days

[redacted]

postvaccination, the participant is to continue completing the e-diary daily until they are symptom free for two consecutive days. Participantswill be provided an injection site reaction measurement tool and shown how to use it to measure the size of certain reactogenicity events associated with vaccination, rate the intensity and where to enter this information in the e-diary (see Section 8.3.5.1).

14. When the participants are discharged from the clinic, they will be reminded:
    - about the diet and activity precautions that must be followed when taking doxycycline (see Section 5.3).
    - to continue to use the antibiotic e-diary to record the times they take their doxycycline doses each day and to use the reactogenicity e-diary to record any vaccination reactions, if applicable; as described in Section 8.3.5.1 (Participant e-diary).

8.1.4.6. Group 2A: Days 9, 22 and 24 (At home)

On Days 9, 22 and 24, the participant is to self-administer doxycycline (100 mg po q 12 hr) at home (at about the same times [± 30 min] each day). The participant will continue with the e-diary as described in Section 8.3.5.1.

It is required that participants self-administer doxycycline on the day before (morning and evening, the day of (evening), and the day after vaccination (morning and evening). The site must contact the participant to remind them to begin their second course of the antibiotics (ie, the site should contact the pariticpant within 24 hours of the anticipated start day for the second course of antibiotics in relation to the scheduled second vaccination date). Any participant who needs to shift their vaccine visit must be reminded to start their doxycycline dosing on the appropriate day, eg, if the second vaccination shifts to Day 22 then the participant will be reminded to start taking doxycycline on the morning and evening of Day 21 in order to meet the dosing requirement.

8.1.4.7. Group 2A: Day 23 (± 1d) – Vaccination # 2

1. Review e-diary entries with the participant, recording doxycycline dosing, discussing any symptoms and if they required any changes in concomitant medications
2. Review and record AEs including any ongoing since prior visit.
3. Reassess concomitant medications.
4. Perform symptom-directed PE, if required.
5. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
6. For WOCBP, collect and perform a UPT (prior to AV7909 vaccination). Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who receive at least one dose of any IP and where conception occurs prior to 12 months after last receipt of any IP will be followed to outcome.
7. Review eligibility for continuing vaccination.

[redacted]

8. Administer AM doxycycline dose; record time of administration in source documents and eCRF.
9. Administer AV7909 vaccination #2; this should occur after doxycycline dosing. Participants should be monitored for at least 30 minutes following vaccine administration for any adverse effects especially anaphylaxis.
10. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate, and temperature) at 30 ± 5 minutes post-vaccination.
11. After diary review, participants will be reminded to continue to use the reactogenicity e-diary and injection site reaction measurement tool to capture reactogenicity events associated with vaccination, any use of concomitant medications and to record the dates, as well as to use the antibiotic e-diary to record times they take their self-administered doxycycline doses; see Section 8.3.5.1 (e-diary).
12. Prior to discharge on Day 23, participants will be reminded
    - of the precautions in Section 5.3.
    - to continue to take their doxycycline the following day
    - to return to clinic in eight days for the third overnight admission.

8.1.4.8. Group 2A: Day 31 (+ 1d) – Evening & Overnight Stay # 3

1. Admit to the clinic for overnight stay #3.
2. Staff will review e-diary entries with participant, checking doxycycline dosing records to document compliance, discuss any t vaccination reactions, as well as the use of concomitant medications, and will remind participants about the precautions associated with the use of doxycycline.

8.1.4.9. Group 2A: Day 32 – Post-vaccine Single Dose Doxycycline PK Session

1. Provide a non-dairy breakfast 30 to 60 min prior to dosing; provide a light lunch and a light dinner/snack over the course of the day.
2. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
3. Collect blood sample for doxycycline t=0 concentration determination prior to administration of AM dose of doxycycline.
4. Administer AM dose of doxycycline following blood sample collection for t=0 concentration determination; ensure the participant remains semi-recumbent for two hours after dosing and continues with a light activity level throughout the day.
5. Blood samples for doxycycline PK assessment are to be collected at the following time points: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post-dose (± 5 min through hr 4, then ± 15 min thereafter).
6. Administer doxycycline 100 mg po in the clinic after the final 12-hour doxycycline PK sample has been collected and 12 hours after morning dose (± 30 min).

[redacted]

7. Following the PK session, staff will assess and record AEs and changes in concomitant medications.
8. When the participants are discharged from the clinic, they will be reminded to continue to use the antibiotic e-diary to record the times they take their doxycycline doses each day and to use the reactogenicity e-diary to record any vaccination reactions, if applicable.

8.1.4.10. Group 2A: Days 33, 34, 35, and 36 – Morning

1. Review e-diary, confirm compliance with doxycycline dosing to document compliance, discuss changes in any vaccination reactions if still ongoing, as well as the use of concomitant medication and remind participants about the dietary and activity precautions that must be followed when taking doxycycline (see Section 5.3).
2. Collect blood samples for determination of doxycycline trough concentrations prior to the in-clinic administration of the AM dose of doxycycline on Days 33, 34, 35 and 36; record times of administration of doxycycline in source document and eCRF.
3. On Days 33, 34, 35 and 36, the evening dose (q 12 hr) of doxycycline is to be self-administered at home (at about the same times [± 30 min] each day).

8.1.4.11. Group 2A: Day 37 – Blood Draw for TNA

1. Collect doxycycline supply, review e-diary dosing entries to confirm compliance with doxycycline dosing to document compliance, discuss changes in the use of concomitant medications, as well as any vaccination reactions, if still ongoing, and remind participants about the dietary and activity precautions that must be followed when taking doxycycline (see Section 5.3).
2. Collect blood sample for determination of doxycycline trough concentrations prior to the in-clinic administration of the AM dose of doxycycline [100 mg po 12 hours after evening dose (± 30 min)]; record time of administration of doxycycline in source document and eCRF.
3. Following doxycycline dose administration, collect blood sample for TNA assessment.
4. Prior to discharge on the morning of Day 37, return doxycycline supply and remind participants to return to clinic that evening for the fourth overnight admission.

8.1.4.12. Group 2A: Day 37 – Evening & Overnight Stay # 4

1. Admit to clinic for overnight stay #4.
2. Staff will review the participant's doxycycline supply and review e-diary entries with participant, checking doxycycline dosing records to document compliance, discuss if they required the use of concomitant medications, as well as any vaccination reactions if still ongoing and will remind participants about the diet and activity precautions that must be followed when taking doxycycline (see Section 5.3).
3. Administer doxycycline 100 mg po 12 hours after morning dose (± 30 min); record time of administration of doxycycline in source document and eCRF.

[redacted]

8.1.4.13. Group 2A: Day 38: – Post-vaccine Steady-State Doxycycline PK Session

1. Provide a non-dairy breakfast 30 to 60 min prior to dosing; provide a light lunch and a light dinner/snack over the course of the day.
2. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
3. Collect blood sample for doxycycline t=0 concentration determination prior to administration of AM dose of doxycycline.
4. Administer AM dose of doxycycline (100 mg po) following blood sample collection for t=0 concentration determination; ensure the participant remains semi-recumbent for two hours after dosing and continues with a light activity level throughout the day.
5. Blood samples for doxycycline PK assessment are to be collected at the following time points: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours post-dose (± 5 min through hr 4 then ± 15 min).
6. Record any reported AEs.
7. Record concomitant medications.
8. Retain doxycycline supply; dose administered before PK session is the final dose.
9. When the participants are discharged from the clinic, they will be reminded to return to the clinic in seven days (nominally Day 51) for the final study visit.
10. Participants should also be reminded that they should still avoid strenuous sports and the sun and use sunscreens until the Day 51 Final In-clinic Study Visit.

8.1.4.14. Group 2A: Day 51 (± 1d) – Final In-Clinic Study Visit

1. Perform complete PE.
2. Review e-diary entries with participant and collect hand-held device if study provided.
3. Review and record AEs.
4. Record concomitant medications.
5. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
6. For WOCBP, collect and perform a UPT. Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who receive at least one dose of AV7909 or doxycycline and where conception occurs prior to 12 months after last receipt of either IP will be followed to outcome.
7. Collect blood samples for hematology and serum chemistry.
8. Collect blood samples for TSH and autoantibodies.
9. Collect urine sample for urinalysis.

[redacted]

8.1.5. Group 2B: Doxycycline + AV7909 without Doxycycline PK Sessions

Shown in Table 8 is a schedule of events for Group 2B participants from screening until the end of the study. Following the table are detailed descriptions of the activities that the sites are expected to conduct for each of the column headings identified in the table. Note that the detailed activities during Screening and Group Assign (Randomization) are covered in Section 8.1.1.

Table 8: Schedule of Events for Group 2B: Doxycycline + AV7909 without Doxycycline PK

	Screening	Group Assign	At Home†	Vac	At Home†	TNA	Final Visit	Safety Calls	EWV USV‡
Study Day(s)	**-28 to -2**	**1**	**2-7**	**8 23***	**9, 22, 24, 32-38**	**37**	**51**	**114, 205, 296, 388**	**NA**
Visit Window ±	**NA**	**NA**		**± 1d**		**± 1d**	**± 1d**	**± 14d**	
Sign, date ICF & assign ID	X								
Review eligibility [a]	X	X		X					
Medical history & demographics	X	X							
Physical examination [b]	X						X		X
ECG [c]	X								
Vital signs [d]	X	X		X			X		X
Pregnancy test [e]	X	X		X			X		X
FSH test [e]	X								
Collect sample for hematology [f]	X						X		X
Collect sample for serum chemistry [g]	X						X		X
Collect sample for urinalysis [h]	X						X		X
Urine drug screen [i]	X								
HIVAb/HBsAg/HCVAb	X								
Concomitant medications [j]	X	X		X		X	X	X	X
Randomize eligible participants		X							
Symptom-directed PE [k]		X		X					
Blood draws for TNA [l]		X				X			
Doxy dosing & compliance [m,n]		X	X	X	X	X			X
AV7909 vaccination [o]				X					
Participant e-diary + tools [p]		X	X	X	X	X	X		X
Staff review of e-diaries [q]			X	X	X	X	X		X
AEs[r], SAEs & AESIs[s]	X	X		X			X	X	X
Collect TSH & autoantibody sample [t]		X					X		X

For the abbreviations used above please refer to Table 1 of the protocol. *The ± 1 d window applies only to the second vaccination on Day 23 (note: the second course of antibiotic treatment will have to shift accordingly). †At Home Days are only those days where both doses of doxycycline are taken at home. ‡For EWV occurring within the visit window of Day 37, a blood sample for TNA will be drawn.

[a] Eligibility will be reviewed before each vaccination, ie, on Day 8 and Day 23.

[b] Physical examinations (PE) will be conducted as described in Protocol Section 8.3.3.

[c] ECGs will be conducted and interpreted at screening as described in Protocol Section 8.3.3.

[d] Vital signs will be administered as described in Protocol Section 8.3.4.

[redacted]

[e] Pregnancy tests (serum and/or urine) will be administered to all WOCBP as described in Protocol Section 8.3.2. Serum pregnancy test will be performed at Screening visit for WOCBP, while urine pregnancy tests for WOCBP will be required before each vaccination. At Screening visit only, FSH test will be performed for postmenopausal women.
[f] Hematology will be conducted as described in Protocol Section 8.3.2.
[g] Serum chemistry will be conducted as described Protocol Section 8.3.2.
[h] Urinalysis will be conducted as described in Protocol Section 8.3.2.
[i] Urine drug screens will be conducted as described in Protocol Section 8.3.2.
[j] Concomitant medications will be identified and recorded as described in Protocol Section 6.5.
[k] Symptom-directed PEs will be conducted as described in Protocol Section 8.3.3.
[l] Blood samples for TNA assessment on Day 1 will be collected in the morning following randomization. Those on Day 37 will be collected after the morning dose of doxy has been administered. A TNA sample will also be collected if EWV occurs within the visit window of Day 37 as described in Protocol Section 8.1.8.
[m] Participants receive their first course of doxy following randomization. Format of the doses and distribution of subsequent courses will be described in the Pharmacy manual. Self-administration of doxycycline starts the following day (Day 2).

Doxycycline dose compliance will be managed as described in Protocol Section 6.4.
[n] Doxycycline doses (100 mg po q 12 hr) will be administered as described in Protocol Section 6.1.4.
[o] Vaccinations with AV7909 will be administered as described Protocol Section 6.1.3.
[p] All participants will be provided with an e-diary for post vaccination follow up along with a thermometer and an injection site reaction measurement tool. Participants in Group 1 and 2 will be provided with an e-dairy for antibiotic compliance. All participants will be trained on the use of these tools and the e-diaries as described in Protocol Section 8.3.5.1.
[q] Staff will begin reviewing the e-diaries on Day 3 and will review them on a routine basis thereafter.
[r] AEs will be collected at all clinic visits through Day 51/EWV as described in detail in Protocol Section 9.
[s] SAEs and potential AESIs will be collected during the Safety Follow-up Telephone Calls (see Protocol Section 8.1.7).
[t] Serum samples for TSH & autoantibody testing will be collected from all participants and tested as described in Protocol Section 8.3.2 (ie, at Day 1, Day 51, and at EWV if the subject received at least one vaccination). Additional samples for TSH & autoantibody testing may be requested (ie, based on the participant's report(s) of a potential AESI); blood draws for additional TSH and/or autoantibody testing should be performed as part of an unscheduled visit.

8.1.5.1. Group 2B: Days 2 to 7 (At home)

1. On Days 2 to 7, the participant will self-administer doxycycline 100 mg po every 12 hours at home at about the same times (± 30 min) each day.
2. Participant will use the e-diary to record the date and time of administration of doxycycline.

8.1.5.2. Group 2B: Day 8 – Vaccination #1

1. Review eligibility.
2. Staff will review the doxycycline supply and review the e-diary entries, conducting a compliance check of the remaining doses compared to the e-diary record. Staff will also discuss any changes in the use of concomitant medication.
3. Review and record AEs.
4. Conduct a symptom-directed PE, if required.
5. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
6. For WOCBP, collect and perform UPT (prior to AV7909 vaccination). Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who receive at least one dose of AV7909 or doxycycline and where conception occurs prior to 12 months after last receipt of either IP will be followed to outcome.

[redacted]

7. Administer doxycycline 500 mg po in AM prior to vaccination; the evening dose of doxycycline 100 mg po will be self-administered at home 12 hours after the AM dose [and at approximately the same time (± 30 min) each day].
8. Administer AV7909 vaccination #1. Participants should be monitored for at least 30 minutes following vaccine administration for any adverse effects especially anaphylaxis.
9. Assess vital signs at 30 ± 5 minutes post-vaccination.
10. Prior to discharge from the clinic, the participant will be given and trained on an e-diary to capture local and systemic reactogenicity events (ie, reactogenicity e-diary) and to record daily for at least seven days following each vaccination. If a reaction is not resolved at seven days postvaccination, the participant is to continue completing the e-diary daily until they are symptom free for two consecutive days. Participants will be given an injection site reaction measurement tool and shown how to use it to measure the size and assess the severity of certain reactogenicity events associated with vaccination. See Section 8.3.5.1 (e-diary) and remind participants about the diet and activity precautions that must be followed when taking doxycycline (see Section 5.3).

8.1.5.3. Group 2B: Days 9, 22 and 24 (At home)

On Days 9, 22 and 24, the participant is to self-administer doxycycline (100 mg po q 12 hr) at home (at about the same times [± 30 min) each day]). The participant will continue with the e-diary as described in Section 8.3.5.1.

It is required that participants self-administer doxycycline on the day before (morning and evening, the day of (evening), and the day after vaccination (morning and evening). The site must contact the participant to remind them to begin their second course of the antibiotics (ie, the site should contact the pariticpant within 24 hours of the anticipated start day for the second course of antibiotics in relation to the scheduled second vaccination date). Any participant who schedules vaccination 2 (on Day 23) to shift within the allowable window (± 1 days) will be reminded to start their doxycycline dosing on the appropriate day, eg, if the second vaccination shifts to Day 22 then the participant will be reminded to start taking doxycycline on the morning and evening of Day 21 in order to meet the dosing requirement.

8.1.5.4. Group 2B: Day 23 (± 1 day) – Vaccination #2

1. Staff will review the participant's doxycycline supply and review e-diary entries, conducting a compliance check of the remaining doses compared to the e-diary record. Staff will also discuss any changes in the use of concomitant medication as well as any vaccination reactions if still ongoing, and reminding the participant of the precautions in Section 5.3.
2. Review and record AEs.
3. Perform symptom-directed PE, if required.
4. Record concomitant medications.
5. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate, and temperature).

[redacted]

6. Review eligibility for continuing vaccination.
7. For WOCBP, collect and perform UPT (prior to AV7909 vaccination). Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who receive at least one dose of any IP and where conception occurs prior to 12 months after last receipt of any IP will be followed to outcome.
8. Administer doxycycline 100 mg po in AM; the evening dose will be self-administered at home.
9. Administer AV7909 vaccination #2; this should occur after doxycycline dosing. Participants should be monitored for at least 30 minutes following vaccine administration for any adverse effects especially anaphylaxis.
10. Following the 30 (± 5) minutes of observation, repeat vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate, and temperature) measurement.
11. After diary review, participants will be reminded to continue to use the reactogenicity e-diary and injection site reaction measurement tool, to capture any use of concomitant medications and to record the dates and times they self-administer their doxycycline doses on the antibiotic e-diary. See Section 8.3.5.1.
12. Prior to discharge on Day 23, participants doxycycline supply will be returned, and participants will be reminded to return to clinic in two weeks (± 1 day) on Day 37 ± 1d for the final blood draws for TNA. Again, participants are to continue dosing with doxycycline through the morning of Day 37.

8.1.5.5. Group 2B: Days 32 to 37 (At home)

On Days 32 to 37, the participant is to self-administer doxycycline 100 mg po every 12 hours at home at about the same times (± 30 min) each day. The participant will continue with the e-diary as described in Section 8.3.5.1. The site must contact the participant to remind them to start their third course of doxycyline within 24 hours of Day 31.

8.1.5.6. Group 2B: Day 37 (± 1) – Blood Draw for TNA

The Day 37 Visit may shift by ± 1 day. If such a shift occurs, the participant must remain on doxycycline 100 mg po every 12 hours until the morning before the blood draw. In the event of such a shift, the participant's required number of doses of doxycycline will vary. The Pharmacy Manual will contain a table detailing the dosing options for the final course of doxycycline given a one-day shift from Day 37.

1. Participants will report to the clinic having taken their morning dose of doxycycline at home.
2. Review participant's doxycycline supply; count the number of remaining doses and compare to the e-diary record to document compliance; record total remaining in source document.
3. Review other e-diary entries with participant. Discuss any changes in the use of concomitant medication as well as any vaccination reactions if still ongoing. Remind

[redacted]

participants that they should still use sunscreens and avoid excessive sun exposure and strenuous sports until the Day 51 Final Study Visit.

4. Record concomitant medications.
5. Collect blood sample for TNA assessment.

8.1.5.7. Group 2B: Day 51 (± 1d) – Final Study Visit

1. Perform complete PE.
2. Review e-diary entries with participant and collect hand-held device if study provided.
3. Review and record AEs.
4. Record concomitant medications.
5. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
6. For WOCBP, collect and perform UPT. Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who receive at least one dose of AV7909 or doxycycline and where conception occurs prior to 12 months after last receipt of either IP will be followed to outcome.
7. Collect blood sample for hematology.
8. Collect blood sample for serum chemistry.
9. Collect blood sample for TSH and autoantibodies.
10. Collect urine sample for urinalysis.

8.1.6. Group 3: AV7909 Alone

Shown in Table 9 is a schedule of events for Group 3 participants from screening until the end of the study. Following the table are detailed descriptions of the activities that the sites are expected to conduct for each of the column headings identified in the table once each participant has received his or her group assignment. Note that for Group 3 this detail only includes Days 8 and 23 as the detailed activities during Screening and Group Assignment (Randomization) were covered previously in Section 8.1.1 and the activities for the Day 37 and Day 51 visits, the Safety Follow-up Phone calls and the EWVs are handled individually in Section 8.1.6.3, Section 8.1.6.4, Section 8.1.7, and Section 8.1.8, respectively.

Table 9: Schedule of Events for Group 3: AV7909 Alone

	Screening	Group Assign	Vac	TNA	Final Visit	Safety Calls	EWV USV‡
Study Day(s)	**-28 to -2**	**1**	**8 23***	**37**	**51**	**114, 205, 296, 388**	**NA**
Visit Window ±	**NA**	**NA**	**±1d***	**±1d**	**± 1d**	**± 14d**	
Sign, date ICF & assign ID	X						
Review eligibility [a]	X	X	X				

[redacted]

	Screening	Group Assign	Vac	TNA	Final Visit	Safety Calls	EWV USV‡
Study Day(s)	**-28 to -2**	**1**	**8 23***	**37**	**51**	**114, 205, 296, 388**	**NA**
Visit Window ±	**NA**	**NA**	**±1d***	**±1d**	**± 1d**	**± 14d**	
Medical history & demographics	X	X					
Physical examination [b]	X				X		X
ECG [c]	X						
Vital signs [d]	X	X	X		X		X
Pregnancy test [e]	X	X	X		X		X
FSH test [e]	X						
Collect sample for hematology [f]	X				X		X
Collect sample for serum chemistry [g]	X				X		X
Collect sample for urinalysis [h]	X				X		X
Urine drug screen [i]	X						
HIVAb/HBsAg/HCVAb	X						
Concomitant medications [j]	X	X	X	X	X	X	X
Randomize eligible participants		X					
Symptom-directed PE [k]		X	X				
Blood draws for TNA [l]		X		X			
AV7909 vaccination [m]			X				
Participant e-diary + tools [n]			X	X	X		X
AEs [o], SAEs & AESIs [p]	X	X	X		X	X	X
Collect TSH & autoantibody sample [q]		X			X		X

For the abbreviations used above please refer to Table 1.

*± 1 d window only applies to the second vaccination (Day 23). ‡For EWV occurring within the visit window of Day 37, a blood sample for TNA will be drawn,

[a] Elibility will be reviewed before each vaccination, ie, on Day 8 and Day 23.

[b] Physical examinations (PE) will be conducted as described in Protocol Section 8.3.3.

[c] An ECG will be conducted at screening as described in Protocol Section 8.3.3.

[d] Vital signs will be administered as described in Protocol Section 8.3.4.

[e] Pregnancy tests (serum and/or urine) will be administered to all WOCBP as described in Protocol Section 8.3.2. Serum pregnancy test will be performed at Screening visit for WOCBP, while urine pregnancy tests for WOCBP will be required before each vaccination. At Screening visit only, FSH test will be performed for postmenopausal women.

[f] Hematology will be conducted as described in Protocol Section 8.3.2.

[g] Serum chemistry will be conducted as described Protocol Section 8.3.2.

[h] Urinalyses will be conducted as described in Protocol Section 8.3.2.

[i] Urine drug screens will be conducted as described in Protocol Section 8.3.2.

[j] Concomitant medications will be identified and recorded as described in Protocol Section 6.5.

[k] Symptom-directed PEs will be conducted as described in Protocol Section 8.3.3.

[l] Blood samples for TNA assessment on Day 1 will be collected in the morning following randomization. Those on Day 37 will be collected in the morning. A TNA sample will also be collected if EWV occurs within the visit window of Day 37 as described in Protocol Section 8.1.8.

[m] Vaccinations with AV7909 will be administered as described in Protocol Section 6.1.3.

[n] All participants will be provided with an e-diary for post vaccination follow up along with d a thermometer and an injection site reaction measurement tool and will be trained on the use of these tools and the e-diary as described in Protocol Section 8.3.5.1.

[o] AEs will be collected at all clinic visits through Day 51/EWV as described in detail in Protocol Section 9.

[p] SAEs and potential AESIs will be collected during the Safety Follow-up Telephone Calls (see Protocol Section 8.1.7).

[q] Serum samples for TSH & autoantibody testing will be collected from all participants and tested as described in Protocol Section 8.1.6.3 (ie, at Day 1, Day 51, and at EWV if the subject received at least one vaccination). Additional samples for TSH &

[redacted]

autoantibody testing may be collected based on the safety follow-up phone contact if warranted from participant report(s) of a potential AESI); blood draws for additional TSH and/or autoantibody testing should be performed as part of an unscheduled visit.

8.1.6.1. Group 3: Day 8 – Vaccination #1

1. Review eligibility.
2. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
3. For WOCBP, collect and perform UPT (prior to AV7909 vaccination). Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who receive at least one dose of AV7909 or doxycycline and where conception occurs prior to 12 months after last receipt of either IP will be followed to outcome.
4. Perform symptom-directed PE.
5. Reassess concomitant medications.
6. Administer AV7909 vaccination #1.
7. Participants should be monitored for at least 30 minutes following vaccine administration for any adverse effects especially anaphylaxis.
8. Assess vital signs at 30 ± 5 minutes post-vaccination.
9. Before the participant is discharged from the clinic, they will be trained on the use of e-diary (see Section 8.3.5.1) and given instructions on how the e-diary should be used to record daily temperature, and any local and systemic reactogenicity events after vaccination. Participants will be instructed to use the e-diary on a daily basis for at least seven days postvaccination. If a reaction is not resolved at seven days postvaccination, the participant is to continue completing the e-diary daily until they are symptom free for two consecutive days.
10. Participants will also be given an injection site reaction measurement tool and shown how to use it to measure the size and rate the intensity of certain reactogenicity events associated with vaccination as well as where to enter this in the e-diary.

Any participant who does not have or who does not wish to use their own personal device to access the e-diary will at this time be supplied a hand-held device by the site.

8.1.6.2. Group 3: Day 23 (± 1 d) Vaccination #2

1. Review participant e-diary discussing any symptoms and any use of pain medications.
2. Review and record AEs.
3. Reassess concomitant medications.
4. Perform symptom-directed PE.
5. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate, and temperature).

[redacted]

6. For WOCBP, collect and perform UPT (prior to AV7909 vaccination). Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who receive at least one dose of AV7909 and where conception occurs prior to 12 months after last receipt of IP will be followed to outcome.
7. Review eligibility for continuing vaccination.
8. Administer AV7909 vaccination #2. Participants should be monitored for at least 30 minutes following vaccine administration for any adverse effects especially anaphylaxis.
9. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate, and temperature) at 30 ± 5 minutes post-vaccination.
10. After diary review the participant will be reminded to use the reactogenicity e-diary and injection site reaction measurement tool to capture the adverse events associated with vaccination, as well as to continue entering their temperatures every day. See Section 8.3.5.1 (e-diary).
11. Prior to discharge following vaccination on Day 23, participants will be reminded to return to clinic in two weeks (± 1 day) on Day 37 ± 1d for the final blood draws for TNA.

8.1.6.3. Group 3: Day 37 (± 1 d) – Blood Draw for TNA

The Day 37 Visit may shift by ± 1 d.

1. Review e-diary entries with participants, discussing any changes in health status and the use of concomitant medication as well as any vaccination reactions if still ongoing.
2. Review and record AEs.
3. Record concomitant medications.
4. Conduct symptom-directed PE (if necessary).
5. Collect blood sample for TNA assessment.

8.1.6.4. Group 3: Day 51 (± 1 d) – Final In-Clinic Study Visit

1. Perform complete PE.
2. Review e-diary entries with participant and collect hand-held device.
3. Review and record AEs.
4. Record concomitant medications.
5. Measure vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
6. For WOCBP, collect and perform UPT. Positive UPTs will be confirmed with a serum pregnancy test. All confirmed pregnancies in participants who receive at least one dose of any IP and where conception occurs prior to 12 months after last receipt of any IP will be followed to outcome.
7. Collect blood sample for hematology.

[redacted]

8. Collect blood sample for serum chemistry.
9. Collect blood sample for TSH & autoantibody determination.
10. Collect urine sample for urinalysis.

8.1.7. Quarterly Safety Follow-up Phone Calls

Following the last scheduled vaccination, the site will conduct quarterly safety follow-ups in which participants are contacted by phone at 3 months (Day 114 ± 14 d), 6 months (Day 205 ± 14 d), 9 months (Day 296 ± 14 d) and 12 months (Day 388 ± 14 d). These phone contacts will be scheduled to key off the participant's actual or, if missed, target Day 23 visit (intended last vaccination day) so that all participants (even those failing to receive both vaccinations but who are followed for safety only) are contacted 3 months after their target Day 23.

The following assessments will be performed over the phone at the 3 months (Day 114 ± 14d), 6 months (Day 205 ± 14 d), 9 months (Day 296 ± 14 d) and 12 months (Day 388 ± 14 d) contacts:

- Assess and document, AEs, SAEs and potential AESIs (refer to Section 9.3)
- For WOCBP, confirm continued use of an adequate method of contraception and inquire about any possible pregnancies (refer to Section 9.4)
- If an AE, SAE and/or an AESI is reported, record any associated medications
- Review the status of ongoing AEs/SAEs/AESIs to update the resolution status

During the telephone calls, the staff member is to inquire about and record in source documentation any AEs and SAEs occurring since either the Day 51 visit or the previous phone contact. Any occurrence of SAEs will be reported to Emergent immediately as specified under Section 9.3 and followed up per procedures described in Section 9.7.2. If an SAE has occurred, it will be recorded on the AE eCRF with any medications taken also recorded on the appropriate eCRF.

During the telephone calls, the staff member will also attempt to elicit and record in source documentation any information on AEs of potential autoimmune etiology. If the condition is a diagnosed or suspected AESI, the staff member may refer the participant to the PI or designee for further phone evaluation if needed; based on initial assessment of potential AESI, the participant will be asked to return for an unscheduled clinic visit for evaluation (refer to Section 8.1.9) and to provide a blood sample for autoantibody testing and/or TSH assessment (if applicable). The PI or designee will obtain records confirming the diagnosis or refer the participant to a medical specialist for additional clinical and diagnostic testing and follow up until the diagnosis is ascertained. The potential AESI will be reported to Emergent immediately as specified in Section 9.3 and followed up per procedures described in Section 9.7.2. Only after the DSMB has assessed the case as a confirmed AESI will the PI or designee record the occurrence of the AESI on the AE eCRF with any medications taken also recorded on eCRFs. The medical monitor or designee will direct the completion of the AE eCRF when communicating the DSMB assessment outcome(s) to the PI or designee.

In the event the site is unable to reach the participant by telephone at any of the interim safety follow-up calls at 3 months (Day 114 ± 14 d), 6 months (Day 205 ± 14 d), 9 months (Day

[redacted]

296 ± 14 d) and 12 months (Day 388 ± 14 d), at least three phone contact attempts must be made before the site documents that the participant was unable to be reached. The contact attempts will be spaced at least one week apart. Failure to reach the participant at one of the interim safety follow-up time points does not preclude contact attempts at the next scheduled safety follow-up time point. Procedures for the final 12-month follow-up call are described in Section 7.4.

8.1.8. Early Withdrawal Visit

Any participant who withdraws early or is discontinued for any reason will be asked to complete an EWV.

1. For participants in Groups 1 and 2, review the participant's remaining antibiotic supply and count the number of remaining doses to document compliance; record total remaining in source document.
2. Perform complete physical examination.
3. Assess vital signs (seated/semi-recumbent blood pressure, heart rate, respiratory rate and temperature).
4. For WOCBP, collect and perform serum pregnancy test.
5. If EWV occurs within the visit window for Day 37, collect blood sample for TNA.
6. Collect blood sample for hematology.
7. Collect blood sample for serum chemistry.
8. Collect urine sample for urinalysis.
9. For participants who have received at least one vaccination, collect blood sample for TSH & autoantibody determination.
10. Review entries in e-diary with participant.
11. Review and record AEs.
12. Record concomitant medications.

8.1.9. Unscheduled Visits

Unscheduled visits will occur when necessary, in the opinion of the PI or designee, to follow-up on an AE or abnormal laboratory test result between scheduled visits. Additionally, participants who report a potential autoimmune-related condition at any of the safety follow-up phone calls will be requested to return to the clinic for an unscheduled visit to provide a blood sample for TSH & autoantibody testing.

Unscheduled visits occurring before Day 51 will include a symptom-directed PE, measurement of vitals, AE (includes SAE/AESI) assessment inclusive of reviewing the status of ongoing AEs since the prior visit, updating of medication usage since the last visit, and (if applicable) review of e-diary data since the last visit.

Unscheduled visits occurring after Day 51 will include an AE/SAE/AESI assessment including blood draw for TSH and autoantibody testing (if medically indicated) and updating of

[redacted]

medication usage since the last visit/contact (only if AE/SAE/AESI-related). Other evaluations performed by the PI or designee during the unscheduled visit as part of the participant's medical care (eg, vital signs, symptom-directed PE, etc) and recommendations given to the participant (eg, referral to the participant's personal physician or specialist for further diagnosis and/or care, prescribed medications) will be documented in the participant's medical chart at the site. In the event of any referrals for further medical care, the PI or designee will follow up with the participant and/or personal physician/specialist to ensure the reporting of any SAEs or potential AESIs per the protocol (refer to Section 9.7.2).

8.2. Immunogenicity/Efficacy Assessments

For all participants, blood samples for the determination of TNA titers will be collected on Day 1 and Day 37 (± 1 d) (2 weeks after the last vaccination). Blood samples will be collected at the EWV only if it falls within the visit window for Day 37.

All immunogenicity laboratory samples will be evaluated using a TNA assay. Specific procedures related to collection, processing, storage, and shipment of the samples will be provided in a Laboratory Manual.

The TNA assay being used in this trial has been validated by Battelle Memorial Institute (Columbus, Ohio) under National Institute of Allergy and Infectious Diseases sponsorship. The assay measures the functional ability of antisera containing anti-PA antibodies to specifically protect cells against *B. anthracis* lethal toxin cytotoxicity {Stinson et al, 2005; Li et al., 2008}. The TNA assay results will be reported as the reciprocal of a serum sample dilution that results in 50% neutralization of lethal toxin cytotoxicity (50% effective dilution; ED_{50}). To standardize assay results, the results are divided by the ED_{50} of a serum reference standard, and the resulting ratio is reported as a 50% neutralization factor, NF_{50}. Reference standard AVR801 will be used.

8.3. Safety Assessments

8.3.1. Adverse Events

Refer to Section 9, Reporting Adverse Events.

8.3.2. Clinical Laboratory Tests

All analytes to be tested during screening/safety/autoimmunity clinical laboratory tests are specified in Table 10. Instructions for the collection, processing, storage, and shipment of screening and safety clinical laboratory test samples are provided separately in the Laboratory Manual. All samples will be sent to the central laboratory for analysis, except urine for pregnancy testing, which will be performed at the site and results documented in the eCRF.

It is the responsibility of the PI or designee to review the results of all screening and safety laboratory tests (including unscheduled lab tests) as they become available, initially for the assessment of study eligibility and subsequently for the continuous safety monitoring of participants. Review of the laboratory reports must be documented.

The following assessments will be performed at Screening only:

- Urine drug screen (refer to Table 10 for analytes).

[redacted]

- Serologic testing (HIV-1/HIV-2 antibodies, HBV surface antigen, and HCV antibody). Confirmatory testing will be performed on any samples that test positive for either HIV or HCV; no additional blood/serum will be required for this confirmatory testing.
- FSH test in postmenopausal women; refer to Section 5.1.

Pregnancy testing will be performed at Screening, immediately following group assignment, before each vaccination, and at the Day 51 Final Study Visit or at the EWV. Female participants who are surgically sterile or are confirmed at Screening to have an FSH level >30 mIU/mL (ie, postmenopausal; refer to Section 5.1) are exempt from pregnancy testing. A serum pregnancy test is required at Screening for all other female participants (ie, WOCBP). Post-screening pregnancy testing in all women not having an FSH level >30 mIU/mL (ie, WOCBP) will consist of a UPT at the above specified visits except for a serum pregnancy test performed at the (if applicable) EWV. All UPTs must be performed at the investigational site and documented to be negative prior to vaccine administration. For participants with positive UPT results, a confirmatory serum pregnancy test will be performed. IP will not be administered to any participant who tests positive for pregnancy. If group assignment occurs within four days of a negative Screening serum pregnancy test, a UPT does not have to be performed.

Blood and urine samples for safety clinical laboratory testing (hematology, serum chemistry, urinalysis) will be collected at Screening and Day 51 as well as at the EWV if the EWV occurs before Day 51. Refer to Table 10 for the list of analytes for hematology, serum chemistry and urinalyses. The laboratory test results will be evaluated against the FDA toxicity grading scale provided in Table 13 of Appendix A.

In addition, blood samples for TSH & autoantibody assessment of ANA, RF and anti-dsDNA will be taken at Day 1 after randomization, Day 51 or EWV or an unscheduled visit if the participant has received at least one dose of vaccine and at the time of safety follow-up phone contact(s) if warranted from participant report(s) of a potential AESI (see Table 10 for the list of analytes for autoantibody testing). These samples will be shipped to the central laboratory and will be banked; testing for TSH and ANA, RF and anti-dsDNA autoantibodies will be performed only if medically indicated (as per PI's discretion based on a report of a potential AESI).

Instructions for the collection, processing, storage, and shipment of laboratory samples will be provided separately in the Laboratory Manual.

It is the PI's responsibility to review the results of all screening and safety laboratory tests (including unscheduled lab tests) as they become available, initially for the assessment of study eligibility and subsequently for the safety monitoring of participants. Review of the laboratory report must be documented.

For each abnormal laboratory test result, the PI needs to ascertain if this is a clinically significant change from screening level for that individual participant. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The PI may repeat the laboratory test and/or request additional tests to verify the results of the original laboratory tests. The PI (or designee) will inform the MM of any unscheduled clinical laboratory testing, including but not limited to confirmatory testing of laboratory samples, with the exception that notification is not required for confirmatory testing for pregnancy, HCV, and HIV.

[redacted]

Investigational sites will be automatically notified of any Grade 3 or higher laboratory abnormalities. For any Grade 3 or higher laboratory result, the test will be repeated as soon as possible by the central lab using the same blood sample to confirm the result. The PI or designee must request the participant return to the clinic for an unscheduled visit for an assessment of clinical status. The decision to redraw laboratory tests will be made by the PI (with notification to the MM) and/or MM and will be based on the type and severity of the laboratory abnormality and the clinical status of the participant. Any Grade 3 or higher neutropenia or lymphopenia must be evaluated with an unscheduled repeat complete blood count (CBC) approximately 72 hours after the initial specimen was drawn.

If the original (retested sample) or repeat laboratory value is Grade 3 or higher or determined by the PI to be a clinically significant change from baseline for that participant, this will be considered an AE and will be recorded on the AE eCRF. Any other clinical laboratory abnormalities must also be reported as AEs if considered by the PI to be a clinically significant change from baseline. If an abnormal laboratory test result is a sign of a disease or syndrome, the disease or syndrome will be recorded as the AE/SAE and not the abnormal laboratory result. Clinical laboratory abnormalities may trigger individual participant or study halting rules (see Section 7.1 and Section 7.3) and may require discontinuation of treatment.

Table 10: Screening/Safety Clinical Laboratory Tests

Hematology	Urinalysis	Viral Serology:
-Basophils	-Appearance	-anti-HCV antibody
-Eosinophils	-Bilirubin	-anti-HIV antibody
-Hematocrit	-Color	-HBsAg
-Hemoglobin	-Glucose	
-Lymphocytes	-Ketones	Urine Drug Screen:
-Monocytes	-Leukocyte esterase	-Amphetamines
-Neutrophils	-Nitrite	-Barbiturates
-Platelets	-Occult blood	-Benzodiazepines
-RBC count	-pH	-Cannabinoids
-WBC count	-Protein	-Cocaine
	-Specific gravity	-Opioids
Serum Chemistry	-Urobilinogen	-
-ALT	-Microscopic examination (only if protein, nitrite, leukocyte esterase, or occult blood results are positive)	
-AST		Autoantibodies
-Bilirubin		-Rheumatoid factor (RF)
-BUN	Additional Tests	-Antinuclear antibody (ANA)
-Creatinine	-FSH (only in postmenopausal women at Screening)	-Anti-double stranded deoxyribonucleic acid (dsDNA) antibodies
-Glucose	-Serum/UPT (all WOCBP)	
	-TSH	

For the abbreviations used above refer to Table 1.

[redacted]

8.3.3. Physical Examination

Complete PEs will be performed at screening, the Final Study Visit (Day 51) and early withdrawal, if applicable. The following will be examined: cardiovascular system (including a standard 12-lead electrocardiogram at screening only, to be read at the site); lymphatic/ hematological, respiratory system; nervous system; skin and appendages; abdominal/gastrointestinal system; metabolic/endocrine, musculoskeletal system; and ear, nose, and throat.

Symptom-directed PEs will be performed at all visits except the Screening, Final Study Visits and early withdrawal (including any unscheduled visits), only if required (ie, in response to the report/collection of AEs/SAEs/potential AESIs).

Abnormal PE findings are to be recorded as AEs if new or changed in severity any time after the first administration of any IP and PE AEs should be assessed for severity and causality. Grade 3 (or higher) PE findings could trigger individual or study halting rules if considered associated with IP administration (see Section 7). Physical examination abnormalities are not separately reported as AEs if the PE abnormality is part of a symptom complex that is already reported as an AE.

8.3.4. Vital Signs

Vital signs including seated/semi-recumbent systolic and diastolic blood pressure, heart rate, respiration rate, and temperature will be obtained at Screening and each subsequent clinic visit through Day 51/EWV (except at AM and PM clinic visits for groups 1A and 2A, and at Day 37 for all groups), including unscheduled visits. Height and weight will only be recorded at Screening. On vaccination days (Days 8 and 23), vital signs will be assessed prior to vaccination and at 30 ± 5 minutes post-vaccination.

All vital sign abnormalities determined by the PI or designee to be a clinically significant change from baseline for that participant should be recorded as AEs. Grade 3 or higher vital signs will be repeated twice to verify that the severity is a Grade 3 or higher. If two of the three assessments are Grade 3 or higher, the vital sign should be reported as a Grade 3 or higher abnormality. Vital sign abnormalities may trigger individual participant or study halting rules (refer to Section 7).

8.3.5. Other Safety Assessments

8.3.5.1. E-diary Records

Participants will be asked to fill out an electronic diary (e-diary) daily for for postvaccination reatogenicity events (all groups) and an e-diary for antibiotic compliance (Groups 1 and 2). Participants who do not have or don't want to use their personal electronics to access the web-enabled e-diary will be provided a hand-held device for purposes of this study. Participants will receive instructions on reactrogenicity and/or antibiotic compliance e-diary completion. Participants will be asked to complete the reactogenicity e-diary at the same time each day to capture observations on the previous 24-hour period. Staff at the clinical site will follow up participant's reactogenicity and/or antibiotic e-diary noncompliance.

[redacted]

There are separate e-diary requirements for this study depending on the treatment group assignment:

- Participants in all three groups will be required to fill out an e-diary to capture reactogenicity events after each vaccination. All participants will receive an injection site reaction measuring tool and an oral thermometer to support in completing the reactogenicity e-diary.
- Participants in Group 1 and Group 2 will be required to also fill out a separate e-dairy to capture antibiotic compliance.

The e-diary to capture reactogenicity events postvaccination will collect the following information:

- each participant's daily oral temperature at the same time each day
- local injection site and systemic reactogenicity events
- whether they have used any pain medications (eg, acetaminophen, aspirin, ibuprofen)

Reactogenicity (solicited systemic and local injection site reactions) will be monitored by the site for at least 30 minutes after vaccination with special attention being paid to signs and symptom of immediate hypersensitivity responses (eg, anaphylaxis, bronchospasm. urticaria, angioedema). Thereafter, local injection site and systemic reactogenicity responses will be assessed daily by participants in their e-diaries for at least seven days following each vaccination. Information will be solicited on the following local injection site reactogenicity reactions: warmth, tenderness, itching, pain, arm motion limitation, redness, lump, swelling, and bruising. In addition, information will be solicited on the following systemic reactogenicity reactions: tiredness/fatigue, muscle ache, headache, and fever (oral temperature). Except for oral temperature, swelling, and redness, the participant will be prompted to grade each reaction according to the grading scale provided below.

- Grade 0 (Absent): Symptom not present
- Grade 1 (Mild): Symptom present but does not interfere with activities of daily living
- Grade 2 (Moderate): Symptom causes some interference with activities of daily living
- Grade 3 (Severe): Symptom prevents activities of daily living or requires medical intervention

Participants will also be asked to respond (yes/no) if they have taken pain/fever medications such as acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs; eg, ibuprofen) or other medication in the past 24 hours. Participants will be directed to not take these types of medications 24 hours before or after vaccinations (refer to Table 3). Investigational site staff will review participant e-diary entries on a routine basis to assess compliance, need for re-instruction and evaluation against individual participant and study halting rules. These reviews will also occur on Day 23 (1 ±d) and Day 37 (1 ±d).

For the assessment of severity of swelling and redness, participants will use the injection site reaction measurement tool to measure redness and swelling at the injection site and then grade these accordingly. The redness grade will be based on greater of the two perpendicular

[redacted]

measurements in centimeters, while swelling grade will be based on greater of the two perpendicular measurements in centimeters and the functional scale (if applicable); see Table 12.

Investigator sites will be notified of any Grade 3 or higher severity scores for follow-up and/or further assessment of symptoms. The site will record verified Grade 3 or higer e-diary reactions as an AE into the AE eCRF. If these reactions start out as mild in severity on a given day, the start date should be recorded as the first date that the reaction is noted as mild in severity. If these reactions end as mild in severity on a given day, the end date should be recorded as the last date that the reaction is noted to be mild in severity. The AE severity will be recorded as the highest severity score within the start and stop dates. If severe reactions reappear in the e-diary after they were absent for one or more days, a second AE will be recorded on the AE eCRF. During follow-up visit(s), the investigator will query the participant about all ongoing e-diary AEs and document the start and stop date of any Grade 3 or higher AEs on the AE page in the eCRF.

If local injection site or systemic reactions continue beyond seven days, participants will be prompted to continue e-diary entries until they are symptom-free for two consecutive days. For any type of reactogenicity persisting two weeks or more, the PI or designee will evaluate the reaction at the next scheduled visit and/or determine based on the nature and severity if a more immediate unscheduled follow-up visit is required to fully assess the reaction. Investigational sites will be alerted of any Grade 3 or higher (eg, ER visit or hospitalization) solicited systemic reactions, which will require discontinuation of vaccinations upon verification by the PI or designee of the Grade 3 or higher status. The PI or designee may require participants reporting Grade 3 or higher reactions to return to the clinic for an unscheduled visit to aid in this evaluation.

In addition to any reaction considered an AE by the PI, solicited reactions reported in the e-diary will be recorded by the PI or designee on the AE eCRF if they are serious (ie, a solicited reaction will be considered 'serious' if confirmed by the investigator to be a Grade 4, or a Grade 3 that upon the investigator's assessment meets any of the SAE criteria outlined in Section 9.1.2); result in discontinuation of study product or withdrawal from the study; or remain unresolved for 14 days or more. Solicited systemic reactions may require discontinuation of vaccinations based on individual participant halting rules (see Section 7.3).

The rating scale to be used for reactogenicity events is the same toxicity grading scale provided in Appendix A, the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* {CBER, 2007}, where symptoms are assessed as Grade 1=mild through Grade 4=potentially life-threatening. Additionally, a Grade of 0 will be available in the e-diary in order to allow the participant to record "symptom not present." For most of the reactogenicity events, there is a direct corresponding symptom entry in the toxicity grading scale (eg, for systemic reactions: fever, headache, fatigue, myalgia; for local reactions: pain, tenderness, erythema/redness, induration/swelling) – refer to Table 12.

For reactogenicity events with no direct corresponding symptom entry in Table 12 (eg, warmth, itching, arm motion limitation, bruising), the grading for "illness or clinical AE" will be used to rate the symptom severity. The symptom-severity descriptions in Table 12 will be translated to lay language in the e-diary instrument to promote participant understanding.

[redacted]

Participants in Groups 1 and 2 will be required to complete e-diary entries to capture their compliance to their antibiotic doses of ciprofloxacin or doxycycline respectively. Participants in these groups will begin e-diary entries as soon as they receive their first dose of antibiotic. The e-diary will remind them to self-administer their antibiotic (ciprofloxacin or doxycycline) at appropriate times and record those times in the e-diary. For those participants receiving an antibiotic, the investigational site staff will review e-diary entries with the participant at every visit overlapping with the antibiotic courses.

8.4. Pharmacokinetics Sessions and Trough Concentrations of Antibiotics

For the participants randomized to Groups 1A or 2A, antibiotic serum concentrations will be measured, and PK parameters will be assessed.

8.4.1. Ciprofloxacin

On days with PK sessions (Days 4, 8, 31 and 35), blood samples for measurement of ciprofloxacin concentrations will be 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 (± 5 min through hr 4, then ± 15 min thereafter).

Blood samples for determination of ciprofloxacin pre-dose or trough concentrations will be collected on Days 4, 5, 6, 7 and 8 and on 31, 32, 33, 34 and 35 prior to administration of the morning ciprofloxacin dose.

8.4.2. Doxycycline

On days with PK sessions (Days 2, 8, 32 and 38), blood samples for measurement of doxycycline concentrations will be 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 (± 5 min through hr 4, then ± 15 min thereafter).

Blood samples for determination of doxycycline pre-dose or trough concentrations will be collected on Days 2, 3, 4, 5, 6, 7 and 8 and on 32, 33, 34, 35, 36, 37 and 38 prior to administration of the morning doxycycline dose.

8.4.3. Specimen Collection, Preparation, Handling, and Shipping

Instructions for the collection, preparation, handling, storage, and shipment of the study samples will be provided in study-specific laboratory manuals.

8.5. Data Safety Monitoring Board

Independent safety oversight will be provided by a DSMB which will be notified of significant AEs (eg, SAEs, severe AEs recorded on the eCRF, potential AESIs of autoimmune etiology, or any other events the medical monitor deems medically relevant) as determined by the medical monitor on an ongoing basis, including any that result in study halt based on prespecified stopping rules (refer to Section 7.1). The DSMB will consist of at least three voting members, one of whom will be an expert in rheumatology/immunology to specifically support the evaluation of potential AEs for autoimmune etiology. The DSMB will make recommendations regarding the safety of continuing enrollment and dosing. Study enrollment and dosing may be

[redacted]

interrupted at the request of the DSMB Chair if it is believed that an AE represents a significant safety concern pending full DSMB evaluation.

The DSMB Chair will receive and evaluate each SAE, each severe AE (reported on the AE eCRF), and potential AEs of autoimmune etiology. The DSMB Chair will determine if an *ad hoc* review by the entire DSMB is necessary. An *ad hoc* review by the entire DSMB, when it occurs, may be focused on a single participant or on data for all participants. The operations of the DSMB will be detailed in a DSMB Charter to be finalized prior to screening of the first participant.

At least one DSMB member will be an expert in autoimmune disorders (eg, rheumatologist, immunologist). This member will review all potential AESIs to assess cases for autoimmune etiology, if preexisting or new onset, and relationship to the IP. Details on the recording of assessment outcomes will be detailed in the DSMB Charter.

9. REPORTING ADVERSE EVENTS

9.1. Definitions

9.1.1. Adverse Event

An AE is any untoward medical occurrence in a participant administered an investigational product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

9.1.2. Serious Adverse Event

A serious AE (SAE) is any untoward medical occurrence at any dose that fulfils one or more of the following:

- Results in death
- Is life-threatening, ie, the participant was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (does not include an event that, had it occurred in a more severe form, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization. (Note: a prescheduled hospitalization is not considered an SAE.)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is another medically significant event that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above (eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, the development of drug dependency or drug abuse)

9.1.3. Adverse Events of Special Interest

For this trial, AESIs are defined as any AE having an autoimmune etiology. Appendix B provides a list of AESI terms defined by FDA's CBER as potentially associated with autoimmune disease that might represent a safety signal for vaccine-associated autoimmunity. Monitoring for late-onset AESIs, ie, those reported after the final visit on Day 51, will extend through 12 months following the last vaccination. Potential AESIs will be evaluated by a member of the DSMB having expertise in this area (refer to Section 8.5). Once assessed as autoimmune in nature, the event will be considered as a confirmed AESI.

9.2. Eliciting and Reporting Adverse Events

AEs (including SAEs and potential AESIs) reported spontaneously by the participant and/or in response to an open question from the PI or designee or revealed by observation (eg, during PE

[redacted]

or from a clinical test result) will be recorded on the AE eCRF if they occurred from the time of the first administration of any IP (Day 2 for Group 2, Day 4 for Groups 1 or Day 8 for Group 3) through Day 51 or EWV, regardless of causal association with the IP. AE reporting is required for any new observation presenting after the first receipt of any IP or for a deterioration of baseline condition (eg, increased severity/frequency). From the signing of the ICF until immediately before the administration of their first IP, only AEs resulting from a study-related procedure will be recorded on the AE eCRF; all other events reported in these time periods will be recorded as signs and symptoms on the Medical History eCRF. If there is any doubt as to whether a clinical or laboratory observation is an AE, the event will be considered an AE and recorded on the AE eCRF. After Day 51 and through the 12-month safety follow-up, AEs, SAEs (meeting definition per Section 9.1.2) and AEs assessed by the DSMB to be of autoimmune etiology (refer to Section 8.5), ie, AESIs, will be recorded on the AE eCRF.

Refer to the specific sections on clinical laboratory tests (Section 8.3.2), PEs (Section 8.3.3), vital signs (Section 8.3.4), and e-diary reactogenicity (Section 8.3.5.1) for details on AE reporting based on participant observation and clinical test results.

9.2.1. Rating the Severity of Adverse Events

All AEs will be assessed for severity by the PI or designee using the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* {CBER, 2007 (refer to Appendix A)}.

The toxicity grading scale has specific grading options for some clinical symptoms, such as nausea/vomiting, diarrhea, headache, fatigue, and myalgia. Any AEs not specifically identified in the Toxicity Grading Scale will use the scale identified for systemic (general) illness or clinical AE. For AEs being reporting from clinical assessments, the PI or designee will refer to the specific sections on clinical laboratory tests(Section 8.3.2), PEs (Section 8.3.3), vital signs (Section 8.3.4), and e-diary reactogenicity (Section 8.3.5.1) on how and when to report AEs and AE severity in applying the toxicity grading scale.

9.2.2. Rating the Causality of Adverse Events

The PI's (or designee's) assessment of an AE's causal relationship to the IP will be documented on the AE eCRF. This causality assessment will be performed only by those study personnel listed on the Delegation of Authority Log as having both the authority and medical training to make such a determination. The following guidelines are provided for this assessment.

1. Unrelated: there is no relationship between either the vaccine or the antibiotic and the reported event.
2. Possibly related to antibiotic (Groups 1 and 2): the event follows a reasonable temporal sequence from the time of antibiotic administration and/or follows a known response pattern to the antibiotic, but could also have been produced by other factors.
3. Possibly related to AV7909 (Groups 1 through 3): the event follows a reasonable temporal sequence from the time of vaccine administration and/or follows a known response pattern to the vaccine, but could also have been produced by other factors.

[redacted]

4. Probably related to antibiotic (Groups 1 and 2): a reasonable temporal sequence of the event with antibiotic administration exists and, based upon the known pharmacological action(s) of the antibiotic, known or previously reported adverse reactions to the antibiotic or class to which the antibiotic belongs (for ciprofloxacin this would be fluoroquinolones and for doxycycline this would be tetracyclines), or the Investigator's clinical judgment, the association of the event with the antibiotic seems likely.
5. Probably related to AV7909 (Groups 1 through 3): a reasonable temporal sequence of the event with vaccine administration exists and, based upon the known action of the vaccine, known or previously reported adverse reactions to the vaccine, or the Investigator's clinical judgment, the association of the event with the vaccine seems likely.
6. Definitely related to antibiotic (Groups 1 and 2): a definite causal relationship exists between antibiotic administration and the AE, and other conditions (eg, concurrent illness, progression/expression of disease state or concurrent medication reaction) do not appear to explain the event.
7. Definitely related to AV7909 (Groups 1 through 3): a definite causal relationship exists between vaccine administration and the AE, and other conditions (eg, concurrent illness, progression/expression of disease state or concurrent medication reaction) do not appear to explain the event.

If the relationship between the AE and the IP is determined to be "possible" or "probable" or "definitely related," the event will be considered to be related to the IP.

9.2.3. Eliciting Adverse Events from Other Safety Assessments

Clinical observations during safety evaluations (ie, PEs, vital signs, clinical laboratory tests) determined by the PI or designee to be abnormal and to represent a clinically significant change from baseline must be reported on the AE eCRF regardless of causal association with the IP. This includes any new observation presenting after the dose of IP (either antibiotic or AV7909) or deterioration of baseline condition (ie, increased severity/frequency) after the first vaccination through Day 51 or EWV. If there is any doubt as to whether a clinical observation is an AE, the event will be considered an AE and recorded on the AE eCRF. Additionally, certain types of observations must be reported by the PI or designee as AEs, as follows (refer to the listed sections below for details on retesting and repeat testing requirements associated with this reporting where applicable):

- Following the dose of any IP, all Grade 3 or higher clinical laboratory abnormalities (sample retested and, if needed, test repeated), unless covered under a disease or syndrome that is already reported as an AE; refer to Section 8.3.2 for details.
- Following the first dose of any IP, all vital sign abnormalities found to be Grade 3 or higher in two out of three assessments (original plus two repeats); refer to Section 8.3.4 for details.

Additionally, while reactogenicity from the e-diary will not be duplicated in AE reporting, the PI or designee will record as AEs any e-diary reactogenicity that is serious, results in

[redacted]

discontinuation of IP or withdrawal from the study, or remains unresolved as of Day 51/EWV (refer to Section 8.3.5.1).

9.3. Immediately Reportable Events

9.3.1. Principal Investigator's Responsibilities

The following events must be reported via email immediately (ie, within 24 hours of awareness), by the site PI or designee to [redacted]:

- Any SAE regardless of causal association with any IP
- Any potential AESI, ie, AE of autoimmune etiology (refer to the list of AESI terms in Appendix B) regardless of causal association with any IP (ie, ciprofloxacin, doxycycline or AV7909)
- Any pregnancy where conception occurred after first exposure to any IP (ie, ciprofloxacin, doxycycline or AV7909) and prior to 12 months after last receipt of either IP

The appropriate form (listed below) will be completed and sent by email to the following address:

[redacted]

For SAEs and AESIs, the Serious Adverse Event and/or Adverse Event of Special Interest Report Form will be completed (abbreviated hereafter SAE Report Form, AESI Report Form). Note that the SAE and AESI Report Form are not the same as the AE eCRF. Accompanying these forms will be source documentation or medical records (eg, discharge summary for hospitalizations, lab reports) which support a diagnosis. Participant identifiers (eg, individual's name, address, telephone number, social security number, medical record number, or hospital/laboratory number) must be redacted from the source documentation.

All SAEs that are unexpected (eg, adverse drug reactions) must be reported to the IRB/IEC as required by ICH GCP E6.

Confirmed pregnancies where conception occurred after first exposure to any IP, and prior to 12 months after last receipt of any IP will be reported to Global PV using the Pregnancy Notification Form. Although normal pregnancy is not an AE, it will mandate discontinuation of IP (refer to Section 9.4).

9.3.2. Sponsor's Reporting Requirements

A SUSAR is a suspected adverse reaction that is both serious and unexpected. As specified in 21 CFR 312.32, SUSARs will be reported by the Sponsor of the Investigational New Drug Application (IND) to the FDA and to all participating PIs in an IND safety report as soon as possible, no later than 15 calendar days after the Sponsor becomes aware of the suspected adverse reaction (21 CFR 312.32(c)(1)).

[redacted]

In addition, any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than seven calendar days after Emergent's initial receipt of the information (21 CFR 312.32(c)(2)).

The Sponsor will report AESIs to FDA within 15 calendar days after becoming aware of the AESI.

9.4. Pregnancy

Prior to trial enrollment, female participants must be advised of the importance of avoiding pregnancy during trial participation and the risks of an unintentional pregnancy. The participant must sign an ICF stating that the risk factors and consequences were communicated.

To be eligible to enroll in the study, any female participant must certify either that she is surgically sterile (ie, had a hysterectomy, bilateral oophorectomy or bilateral salpingectomy), postmenopausal (defined as >12 consecutive months without menses and Screening FSH >30 mIU/mL) or has been using an effective method of birth control for at least one month prior to Day 1. Methods of acceptable birth control are listed in Section 5.1. Additionally, WOCBP randomized to Groups 1 and 2 must be willing to add a double barrier method of birth control if they are not surgically sterile or postmenopausal, and their primary method of birth control is hormonal or an IUD.

All women will have a serum pregnancy test performed at screening and at the EWV, if applicable, unless they are postmenopausal (confirmed with FSH >30 mIU/mL at screening) or indicate that they are surgically sterile. All WOCBP will also receive a UPT within 24 hours prior to each AV7909 vaccination. Vaccinations will not be administered to participants who test positive for pregnancy.

In addition, a UPT will be performed on the Day 51 for WOCBP participants in all groups. Positive UPTs will be confirmed with a serum pregnancy test. Pregnancy is not considered an AE in this study. If a participant's pregnancy is detected between Randomization and Day 2, no IP is to be administered and the participant is to be withdrawn from the study.

If a participant becomes pregnant at any time after Day 2, (ie, after receipt of at least one dose of either IP), and where conception occurs prior to 12 months after last receipt of either IP, the pregnancy is to be reported within 24 hours of awareness by completing the Pregnancy Notification Form and forwarding it to the Global Pharmacovigilance Department (see Section 9.3.1). No further IP will be administered to the participant. Participants will also be encouraged to continue planned safety follow-up in the study.

All pregnancies occurring after Day 2 (ie, after receipt of at least one dose of either IP), and where conception occurs prior to 12 months after last receipt of either IP are to be followed to outcome (eg, delivery, spontaneous abortion, or therapeutic abortion), including after the study is completed. When the PI becomes aware of the outcome of the pregnancy, a Pregnancy Outcome Form will be completed and forwarded to the Global Pharmacovigilance Department by email (see Section 9.3.1) within 24 hours of awareness. A pregnancy outcome of spontaneous miscarriage, congenital anomaly or birth defect is considered an SAE and must be reported according to the procedures described in Section 9.3.1 above. As applicable, contact will be made when the infant is ~28 days old for a final follow-up.

[redacted]

9.5. Reporting of Other Information – Unanticipated Problems

As outlined by the Office for Human Research Protection (OHRP), unanticipated problems must be reported to the IRB according to the requirements of 45 CFR Part 46. Unanticipated problems are considered to include any incident, experience, or outcome that meets ALL of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
  - Procedures that are described in the study-related documents, such as the IRB approved research protocol and informed consent document.
  - The characteristics of the participant population being entered into the study.
- Related or possibly related to participation in the study which means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the sample collection.
- Suggests that the study places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An incidence, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the study or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of participants or others. Only a small subset of AEs occurring in human subjects participating in a clinical study will meet these three criteria for an unanticipated problem. There are other types of incidents, experiences, and outcomes that occur during the conduct of clinical study that represent unanticipated problems but are not considered AEs. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with AEs. In other cases, unanticipated problems place participants or others at increased risk of harm, but no harm occurs.

The investigator should promptly notify the IRB when an unanticipated problem involving risks to participants or others is identified. Also, the investigator should notify Emergent and CRO of unanticipated problem(s).

9.6. Procedure for Breaking the Blind for Individual Participants

Not applicable to this study.

9.7. Follow-up of Adverse Events

9.7.1. Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified on or before the last scheduled visit (Day 51 or EWV) must be followed through and recorded on the AE eCRF. All nonserious events that are ongoing at Day 51 or EWV will be recorded with the current status noted as “Not Recovered/Not Resolved” on the AE eCRF. The status of ongoing, previously reported AEs will be reviewed at the Day 51/EWV to determine if resolved. For participants that continue in the study beyond Day 51, the

[redacted]

status of ongoing AEs will be queried at the quarterly phone contacts to determine status and update the resolution status in the AE eCRF.

9.7.2. Follow-up of Serious Adverse Events or Adverse Events of Special Interest

Participants experiencing SAEs or AESIs will be followed clinically until their health has returned to normal and all parameters have returned to baseline or has otherwise been explained or they have been referred to outside care. It is expected that the PI or designee will provide or arrange appropriate supportive care for the participant. Withdrawals of participants from treatment and/or the trial are at the discretion of the PI or designee, according to the guidance provided in Section 7.3.

All SAEs/AESIs will be followed by the PI or designee until one or the other condition is met:

- The SAE/AESI is resolved or stable if expected to remain chronic.
- The participant is referred to a specialist or other physician for treatment and follow-up. The PI or designee will follow events even if the participant is seen by another physician. The PI or designee will follow-up with the participant and the participant's physician to obtain information about the event outcome and any treatments and medications administered for the event.

The following will be considered acceptable reasons for discontinuation of follow-up of ongoing SAEs/AESIs:

- Participant withdraws consent.
- Participant is referred to appropriate long-term medical care.
- Participant is considered lost to follow-up (refer to Section 7.4 for description of contact attempts before a participant may be deemed lost to follow-up).

It is expected that the clinical site will obtain supporting medical records from appropriate physicians and record this information on the SAE/AESI Report Form (refer to Section 9.3) and AE eCRF. Additional information received related to any SAE/AESI must be forwarded within 24 hours of awareness to the Emergent Global PV Department.

[redacted]

10. STATISTICAL ANALYSIS

10.1. Study Endpoints and Statistical Hypotheses

10.1.1. Primary Endpoints

To assess whether co-administration of AV7909 with antibiotics affects antibiotic PK profiles, equivalence tests on the PK parameters ($AUC_{0\text{-}12h}$ and C_{max}) at steady state pre- and post-vaccination will be carried out separately for ciprofloxacin and doxycycline using PK data collected from subjects from independent study groups (Group 1 for ciprofloxacin, Group 2 for doxycycline).

For each of the primary endpoints (for each of the two antibiotics), the equivalence tests on PK parameters ($AUC_{0\text{-}12h}$ and C_{max}) at steady state pre- and post-vaccination will be performed. Therefore, demonstration of non-interference of steady state PK is defined separately for each antibiotic and there is only one way to meet the primary endpoint for each antibiotic.

Specifically, for each antibiotic, the null hypotheses are:

- $AUC_{0\text{-}12h}$: The geometric mean of the within-participant ratios of post-vaccination (Day 35 for ciprofloxacin and Day 38 for doxycycline) over the pre-vaccination (Day 8) $AUC_{0\text{-}12h}$ will be greater than 1.25 or less than 0.80.
- C_{max}: The geometric mean of the within-participant ratios of the post-vaccination (Day 35 for ciprofloxacin and Day 38 doxycycline) over the pre-vaccination (Day 8) C_{max} will be greater than 1.25 or less than 0.80.

The null hypothesis will be rejected when the 90% confidence intervals (CIs) of the geometric mean of the within-participant ratios is contained entirely within the equivalence bounds of [0.8, 1.25]. For each antibiotic, to conclude that administration of two-dose regimen of AV7909 does not affect the steady state of PK profile, the null hypotheses should be rejected for both endpoints $AUC_{0\text{-}12h}$ and C_{max}.

10.1.2. Secondary Endpoints

10.1.2.1. Secondary Safety Endpoints

- Incidences of AEs from the first dose of any IP through the Final Study Visit (Day 51 ± 1 d)
- Incidences of serious AEs (SAEs) from the first dose of any IP until the 12-month follow up (Day 388 ± 14 d)
- Incidences of solicited systemic and injection site reactions reported in participant e-diaries following each vaccination
- Incidences of AESIs from the first dose of any IP until the 12-month follow up (Day 388 ± 14 d)
- Incidences of clinical laboratory abnormalities

No hypothesis testing is planned for any of the safety endpoints.

[redacted]

10.1.2.2. Secondary Pharmacokinetic Endpoints

To determine if the single-dose PK values of either ciprofloxacin or doxycycline are affected by AV7909 vaccination, separate equivalence tests will be carried out in parallel for each antibiotic in the similar manner as the primary PK analyses:

- $AUC_{0\text{-}12h}$: Geometric mean of within-participant ratios of post-vaccination (Day 31 for ciprofloxacin and Day 32 for doxycycline) over the pre-vaccination (Day 4 for ciprofloxacin and Day 2 for doxycycline) $AUC_{0\text{-}12h}$ is greater than 1.25 or less than 0.8.
- C_{max}: Geometric mean of within-participant ratios of post-vaccination (Day 31 for ciprofloxacin and Day 32 for doxycycline) over the pre-vaccination (Day 4 for ciprofloxacin and Day 2 for doxycycline) C_{max} is greater than 1.25 or less than 0.8.

No hypothesis testing is planned for the secondary PK endpoints, which will be evaluated and reported for information only.

10.1.2.3. Secondary Immunogenicity Endpoints

To evaluate whether the co-administration of antibiotics affects the immune response after two IM doses of AV7909, a non-inferiority test will be conducted independently for ciprofloxacin and doxycycline. Specifically, the null hypotheses are:

- For ciprofloxacin: the geometric mean ratio of TNA NF_{50} values at Day 37 for Group 1 over Group 3 will be less than or equal to 0.5
- For doxycycline: the geometric mean ratio of TNA NF_{50} values at Day 37 for Group 2 over Group 3 will be less than or equal to 0.5

The null hypothesis will be rejected when the lower bound of the two-sided 95% CI of the geometric mean ratio of TNA NF_{50} values is greater than 0.5.

For each antibiotic, the formal hypothesis testing for the secondary immunogenicity endpoints will only be carried out after the primary PK endpoint has been met for the corresponding antibiotic. If the primary PK endpoint for an antibiotic is not met, the corresponding secondary immunogenicity endpoints will be provided for information only.

10.2. Sample Size and Power

The sample size for this study was selected based on both the primary and secondary endpoints.

The assessment as to whether vaccination with AV7909 affects the PK of either ciprofloxacin or doxycycline will be made based on the geometric mean of the within-participant ratios (post-vaccination over pre-vaccination) of $AUC_{0\text{-}12h}$ and C_{max}. The equivalence margin for the geometric mean ratio is [0.80, 1.25], which will be compared with the 90% CI for the geometric mean of within-participant ratios of $AUC_{0\text{-}12h}$ and C_{max}. Assuming the coefficient of variation (CV) is 30% for geometric mean ratio and the true geometric mean ratio is 0.95, 27 participants allow for 90% power to reject the null hypothesis at a significance level of 5%. A group size of 40 participants for Group 1A (AV7909 + ciprofloxacin with PK) or Group 2A (AV7909 +

[redacted]

doxycycline with PK) is planned to allow for up to 30% of participants being excluded from the PK population.

A sample size of 53 in each of the IP groups (Group 1 = AV7909 + ciprofloxacin, Group 2 = AV7909 + doxycycline, Group 3 = AV7909 only) provides 90% power at the 2.5% one-sided significance level for the non-inferiority test, defined as the lower bound of the two-sided 95% CI of the geometric mean ratio of the AV7909 + antibiotic over the AV7909 only (Group 1 vs. Group 3, Group 2 vs. Group 3) greater than 0.5. This assumes that the true geometric mean ratio between the two groups is 0.85 and the CV of TNA NF_{50} values in each group is 100%. A total of 70 per IP group is planned to allow for up to 25% of drop-out rate.

The sample size calculation was performed using SAS 9.4 statistical software.

10.3. Analysis Populations

There will be four analysis populations for this study:

The Intent-to-treat (ITT) Population will include all participants who are randomized. Participant disposition and baseline demographics will be summarized by IP group (Groups 1, 2 and 3) for the ITT population according to the group into which the participant is randomized.

The Safety Population will include all randomized participants who receive at least one dose of either antibiotic or AV7909. All the safety analyses will be conducted with the Safety Population according to the treatment they received.

The PK Population will include all participants in Group 1A and Group 2A who:

- Received two doses of AV7909 according to the protocol (eg, correct dose no temperature excursion, and within the study-specified windows)
- If in Group 1A, received at least 5 of the 7 in-clinic ciprofloxacin doses between Day 4 through the morning of Day 8 and between Day 31 through the morning of Day 35; or if in Group 2A, received at least 7 of the 9 in-clinic doxycycline doses between Day 2 through the morning of Day 8 and between Day 32 through the morning of Day 38
- Have adequate data for PK analysis for the calculation of $AUC_{0\text{-}12h}$ and C_{max} at the Day 8 (both Group 1A and 2A) and Day 35 (Group 1A) or Day 38 (Group 2A) visits,
- Have no protocol deviations that would affect ciprofloxacin or doxycycline PK

Exclusion of participants from population will be done on a case-by-case basis at the time of the PK parameter analysis.

The PK Population will be used for all PK analyses. Participants will be included in the treatment group (ciprofloxacin or doxycycline) according to the antibiotic they received.

The Immunogenicity Population will include all randomized participants who meet the following criteria:

- Received two AV7909 vaccinations according to the protocol (eg, correct dose, no temperature excursion, and within the study-specified windows)

[redacted]

- Had a valid immunogenicity (TNA) result at Day 1 (pre-vaccination) showing no evidence of previous exposure to anthrax or an anthrax vaccine (ie, TNA below the limit of detection)
- Had a valid immunogenicity (TNA) result at Day 37, within the study specified window
- Participants in Group 1 or 2 should have taken at least 50% of the protocol-specified antibiotic doses

The Immunogenicity Population will be used for the immunogenicity analyses. Participants will be included in the IP group (Group 1, 2 and 3) according to the treatment they actually received.

10.4. Handling of Outliers and Missing Data

Individual serum concentrations or entire serum concentration-time profiles for a participant may be excluded from the analysis at the discretion of the pharmacokineticist following a review of available documentation (eg, bioanalytical report, validation report, protocol deviation log) and communication with the sponsor. Any such exclusion will be clearly listed in the clinical study report along with justification for exclusion. Any excluded outlier data should be flagged in the individual data listings.

Missing PK samples or antibiotic concentration values or missing immunogenicity response TNA NF_{50} values will be handled as described in the Statistical Analysis Plan (SAP). Antibiotic concentrations reported as below the lower limit of quantification (< LLOQ) will be handled as specified in the SAP. Non-missing TNA NF_{50} values reported as < LLOQ will be handled as specified in the SAP.

10.5. Statistical Methods

10.5.1. PK Analyses

10.5.1.1. Summary of Concentrations and PK Parameters

Summary statistics for serum concentrations of ciprofloxacin and doxycycline will be tabulated by time point and study day. Summary statistics will be provided for trough concentrations of ciprofloxacin and doxycycline by study day. The PK parameters shown in Table 11 will be derived from the concentration-time data by noncompartmental analysis methods and summarized by study day.

Table 11 Antibiotic Pharmacokinetic Parameters

Variable	Definition
C_{max}	Maximum observed serum concentration
t_{max}	Time of maximum observed serum concentration
$t_{1/2}$	Elimination half-life (calculated as ln 2/ K_{el})
K_{el}	Elimination rate constant

[redacted]

Variable	Definition
$AUC_{0\text{-}12h}$	Area under the serum concentration-time curve (12 hours)
AUMC	Area under the first moment curve
$AUC_{0\text{-}inf}$	Area under the serum concentration-time curve extrapolated to infinity
MRT	Mean residence time

10.5.1.2. Equivalence Testing for Primary PK Endpoints

The goal of the study with the primary PK endpoints is to demonstrate that vaccination with AV7909 does not affect the steady-state PK profiles of either ciprofloxacin or doxycycline. The equivalence testing will be constructed using paired two one-sided t-tests (TOST) to provide the point estimate and 90% CIs for geometric mean of the within-participant ratios of the steady-state values of $AUC_{0\text{-}12h}$ and C_{max} post two doses of AV7909 (Day 35 for ciprofloxacin and Day 38 for doxycycline) vs. pre-vaccination of AV7909 (Day 8 for ciprofloxacin and doxycycline). To conclude that AV7909 vaccine has no effect on the steady state PK for ciprofloxacin or doxycycline, the 90% CIs should fall entirely within the equivalence range of [0.80, 1.25] for both endpoints $AUC_{0\text{-}12h}$ and C_{max}.

To demonstrate that antibiotic concentrations have achieved steady state, the trough value analysis will be performed using the stepwise testing for linear trend, the application of the NOSTASOT (No Statistical Significance Of Trend) methodology proposed by {Maganti et al, 2008}. The details of the calculation will be provided in the SAP.

10.5.1.3. Equivalence Testing for Secondary PK Endpoints

The secondary PK analyses will be performed to evaluate the effect of vaccination with AV7909 on the single-dose PK profile for either ciprofloxacin or doxycycline. The equivalence tests will be conducted in a similar statistical manner as the primary analyses. If the 90% CIs for geometric mean of the within-participant ratios of the single-dose values of $AUC_{0\text{-}12h}$ and C_{max} post two doses of AV7909 (Day 31 for ciprofloxacin and Day 32 for doxycycline) vs. pre-vaccination of AV7909 (Day 4 for ciprofloxacin and Day 2 for doxycycline) fall entirely within the equivalence range of [0.80, 1.25] for both endpoints, $AUC_{0\text{-}12h}$ and C_{max}, it will be concluded that the AV7909 vaccine has no effect on the single dose PK for ciprofloxacin or doxycycline.

10.5.2. Non-Inferiority Testing for Secondary Immunogenicity Endpoints

Two-sided 95% CIs will be calculated for the geometric mean ratio of TNA NF_{50} values at Day 37 between the AV7909 + antibiotic group and the AV7909 only group (Group 1 vs. Group 3, Group 2 vs. Group 3). To conclude that ciprofloxacin or doxycycline does not reduce the immune response to AV7909, the lower bound of the 95% CI should be greater than the non-inferiority margin of 0.5.

10.5.3. Exploratory Analysis for Immunogenicity

To evaluate the possible impact on the immunogenicity endpoints of a population not balanced by age and gender, exploratory analyses will be conducted using linear regression to compare the

[redacted]

immunogenicity response at Day 37 between each AV7909 + antibiotic group and the AV7909 only group, ie, between Group 1 (AV7909 + ciprofloxacin) and Group 3 (AV7909) and between Group 2 (AV7909 + doxycycline) and Group 3 (AV7909). In the linear regression models, the stratification factor, study site, will be included in the model as a random effect; participant sex and age will be included as fixed factors with age being dichotomized into ≤30 and >30. The adjusted GMT ratios for the TNA NF_{50} values will be provided with 95% CI.

10.6. Safety Analysis

All safety data will be presented in the form of tabulations and listings, based on the Safety Population. Data summaries will be tabulated by treatment group (Ciprofloxacin only, AV7909 + ciprofloxacin, Doxycycline only, AV7909 + doxycycline, AV7909 only, and Total, ie, all participants receiving any IP) as specified in Section 10.3. Continuous variables will be summarized using number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by the number (frequency) and percentage in each category. No formal hypotheses testing will be conducted for safety data.

10.6.1. Adverse Events

All AEs will be coded to SOC and PT according to MedDRA. Treatment-emergent adverse events (TEAEs) are defined as AEs that present after the initiation of treatment or any AEs already present that worsen in either intensity or frequency following treatment. The incidences of TEAEs will be presented in tabular form by MedDRA coded terms of SOC and PT, and by severity (toxicity grade), seriousness, relationship to IP, and outcome (death, discontinuation of IP, study withdrawal) for each treatment group. A tabulation will be provided of TEAE incidences by MedDRA PT in decreasing frequency of the "AV7909 Total" column. Separate tabulations by MedDRA SOC and PT will be provided for SAEs and AESIs determined to be of autoimmune etiology based on decision of the DSMB. Participants having the same TEAE more than once will be counted in tabulations once for each PT and once within each SOC at the maximum severity and relatedness. The incidences of AEs from the first dose of any IP through the Final Study Visit (Day 51 ± 1d), as well as incidences of AEs from the first dose of any IP up to 12-month follow-up will be tabulated separately as appropriate.

10.6.2. Clinical Laboratory Data

Safety clinical laboratory results will be tabulated by visit and group and listed by individual participant. Observed values and changes from baseline of continuous laboratory variables (hematology, serum chemistry, and selected urinalysis parameters [eg, specific gravity]) will be summarized using descriptive statistics (n, mean, median, SD, minimum, and maximum). Observed values of categorical laboratory variables (eg, urinary protein), incidences of abnormalities by analyte according to laboratory normal ranges and highest toxicity grade (refer to Table 13 in Appendix A), and shifts from baseline will be summarized descriptively (number and percentage) by visit and treatment group. Shift tables will be produced to reflect shifts from baseline values against the lab normal ranges (low, normal, high) as well as against toxicity grading criteria (Grade 0, Grade 1, Grade 2, Grade 3, Grade 4). Note: Grade 0 = laboratory value within normal range or laboratory value does not meet criteria for toxicity of at least Grade 1

[redacted]

(refer to Table 13 in Appendix A). Screening (serology, urine drug screen, FSH) and pregnancy test results will be listed by individual participant.

In tabulations, the last measurement before the first IP administration will be used as the baseline value. In listings, laboratory values outside of the reference range will be flagged: L=low compared to the lower limit of the normal range, H=high compared to the upper limit of the normal range. Additionally, laboratory abnormalities associated with a severity grade based on the toxicity grading criteria (refer to Table 13 in Appendix A) will be flagged: Grade 1 = Mild, Grade 2 = moderate, Grade 3 = severe, and Grade 4 = potentially life-threatening. Grade 3 or higher laboratory abnormalities will be summarized in a separate listing.

10.6.3. Physical Examination

Complete PE and symptom-directed PE data will be tabulated (number of participants with normal/abnormal findings by body system and group) and listed by individual participant.

10.6.4. Vital Signs

Vital signs data will be tabulated by visit and treatment group and listed by individual participant. Observed values and changes from baseline in vital signs will be summarized descriptively (n, mean, median, standard deviation, minimum, and maximum; incidence of abnormality according to highest toxicity grade). Baseline is defined as the last measurement before the first IP administration. In listings, vital sign abnormalities associated with a severity grade based on the toxicity grading criteria (refer to Table 12 in Appendix A) will be flagged: Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, and Grade 4 = potentially life-threatening.

10.6.5. Prior and Concomitant Medications

Medications will be coded according to the World Health Organization's (WHO) WHO Drug Global Dictionary and daily dosages normalized. Data will be tabulated and listed by individual participant according to study period (prior medications taken before the first IP administration, concomitant medications taken after the first IP administration) and treatment group.

10.6.6. Other Safety Variables

10.6.6.1. Reactogenicity

In-clinic and e-diary reactogenicity data will be tabulated using descriptive statistics (number and percentage of participants reporting a reaction) for any symptom and each individual symptom by vaccination, treatment group, and severity grade. During the assessment period post each vaccination, when the severity differs across the daily assessments for a symptom, the maximum severity will be shown in summary tables.

10.6.6.2. Autoantibody Testing and TSH Assessment

Samples taken for TSH assessment and for RF, ANA and anti-ds DNA antibodies will be banked and will only be tested if medically indicated (ie, as per PI's discretion based on a report of

[redacted]

potential AESI). Results will be tabulated with negative/positive results by study visit and listed by individual participant.

10.7. Interim Analysis

No interim analyses are planned in this study.

10.8. Multiplicity

In this phase 2 study, multiplicity adjustment is not planned. All the PK and immunogenicity endpoints are evaluated in parallel for the two antibiotics, ciprofloxacin and doxycycline.

The primary PK endpoints for each antibiotic will be met when the 90% CIs of the geometric mean of ratios for both $AUC_{0\text{-}12h}$ and C_{max} are contained entirely within the equivalence bounds of [0.8, 1.25]. Since both parameters must satisfy the equivalence condition and each equivalence test is conducted at 5% level, the overall type I error rate is controlled at less than 5%.

For immunogenicity, non-inferiority is evaluated as a one-sided test at 2.5% level. As a secondary endpoint, the test will only be formally evaluated when the corresponding primary PK endpoints have been met. Otherwise the results will be provided for information. No adjustment for multiplicity is required based on the closed test procedure.

No other formal hypothesis testing will be carried out. The secondary PK endpoints (single dose) will be evaluated and reported for information only.

10.9. Final Analysis Plan

A Statistical Analysis Plan (SAP) will be finalized prior to clinical database lock [to include data up to and including last subject's last in-clinic visit (Day 51; ie, four weeks after second vaccination)]. Clinical Study Report (CSR) will be generated with data up to and including last subject's last in-clinic visit (Day 51). All data after Day 51 (ie, data up to and including last subject's 12-month safety follow up telephone call) will be included as an addendum to the CSR. Details of the statistical methods and analyses will be provided in the final SAP.

[redacted]

11. DATA HANDLING AND RECORD KEEPING

11.1. Source Documents and Access

Source documents are defined as the records of original observations and activities of a clinical investigation. Source documents will include but are not limited to screening logs, progress notes, clinical and office charts, hospital records, pharmacy dispensing records, laboratory notes, e-diary data, safety laboratory data including both local and central laboratory data, memoranda, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the PI(s) and made available for direct inspection and copying by authorized persons. Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as specified in the ICF.

11.2. Data Management

A validated, electronic data capture (EDC) system will be used during the trial. The data management functions for the study will be outsourced to a CRO. Data management activities to be performed for the study will be described in detail in the Data Management Plan documents. The standard operating procedures (SOPs) governing data management activities will be mutually agreed upon by the CRO and Emergent and documented in these DMP documents. Emergent is responsible for the oversight and management of the CRO.

11.3. Data Collection and Discrepancy Management

Data collected during the study will be recorded in the eCRFs designed for this study. Investigational sites will have the responsibility for capturing and maintaining accurate eCRF data, records, and relevant source documentation, as well as conforming to procedures established by the CRO/Emergent around system access/security and ensuring a data audit/edit trail for data corrections. All source documents will be verified by the CRO study monitor for accuracy. Information from external sources such as laboratory data, images, etc. as defined in this protocol will be collected and maintained outside the EDC and reconciled with the eCRF data periodically. As data are entered into the eCRF, automated edit checks will validate data. Additionally, manual reviews will be performed for data discrepancy by the CRO and queries will be generated into the EDC system. After clinical sites respond to queries and data corrections are made and reviewed by the CRO, the PI will review and electronically sign the eCRF for each participant. The CRO and Emergent will review data for accuracy, completeness, and consistency during the conduct of the study and prior to database lock.

11.4. File Management at the Investigational Site

The PI will ensure that the trial center file is maintained in accordance with the ICH Guideline and as required by applicable local regulations. The PI/institution will take measures to prevent accidental or premature destruction of these documents.

11.5. Record Retention at the Investigational Site

Per ICH guidelines, study documents will be retained for one of the following periods:

- A period of at least two years after the date of the last approval of a marketing application in an ICH region until there are no pending or contemplated marketing applications;
- A period of at least two years after Emergent has notified the regulatory authority(ies) that clinical investigation with this product is discontinued.

The PI must not dispose of any records relevant to this trial without either (1) written permission from Emergent or (2) provision of an opportunity for Emergent to collect such records. The PI will be responsible for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial, including any data queries received from the Sponsor or designee. Such documentation is subject to inspection by Emergent and relevant regulatory agencies. If the PI withdraws from the trial (eg, due to relocation or retirement), all trial-related records will be transferred to a mutually agreed upon designee within an Emergent-specified timeframe. Notice of such transfer will be given to Emergent in writing.

11.6. Protocol Deviations

The PI or site staff may not deviate from the protocol except, in rare circumstances, as necessary to eliminate immediate hazards to the trial participants. In such event, both the Sponsor and IRB/IEC will be immediately notified, no more than 24 hours after the deviation is implemented.

It is the responsibility of the PI to comply with the protocol. A deviation occurs when site personnel or a participant does not adhere to the protocol's stipulated requirements, whether inadvertently or planned. The occurrence of protocol deviations will be routinely monitored by the CRO and Sponsor for evaluation of PI compliance with the protocol, GCP, and regulatory requirements. The PI or designee will inform the IRB/IEC of all protocol deviations according to the requirements of each IRB/IEC. Deviations may be identified during the course of the study by the PI or site staff, study monitor during routine or directed monitoring visits (recorded in monitoring reports), and Sponsor or BARDA personnel. In compliance with GCP, all identified protocol deviations will be documented – entered in the CRO's Clinical Trial Management System or equivalent – and classified according to procedures outlined in the protocol deviation plan. Deviations will be assessed by the CRO and Sponsor to identify appropriate corrective and preventive actions and followed up to ensure renewed understanding and proper execution of the protocol.

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, participant dosing error, treatment assignment error, participant enrolled in violation of eligibility criteria, violation of concomitant medication use restriction), the PI or designee will contact the MM at the earliest possible time by telephone, or the reverse as applicable. The PI and MM will come as quickly as possible to a joint decision regarding the participant's continuation in the trial. This decision will be documented by the PI and MM and reviewed by the site monitor.

Continued protocol deviations despite re-education of investigational site personnel, or persistent protocol deviations that are reportable to regulatory agencies may result in discontinued shipment of IP and termination of further enrollment at the investigational site, or termination of the investigational site from the study.

[redacted]

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Monitoring

The site will be monitored at regular intervals using a risk-based monitoring approach to ensure compliance with the protocol, ICH GCP, applicable regulatory requirements, and current SOPs of the CRO and Emergent. Sites will be monitored both remotely and in-person to ensure the integrity of the data collection and the safety of study participants. A medical monitoring plan will be established, and data will be reviewed on a monthly basis. A Monitoring Plan, containing the frequency on-site and remote monitoring visits conducted by the CRO study monitors as well as monitoring requirements and contact details of the CRO study monitors will be developed and followed throughout the study.

As a representative of Emergent, the CRO study monitors will visit the site periodically. In addition, the CRO study monitors will be available between visits via telephone and email as needed. The CRO study monitors will perform the following functions:

- Provide information and support to the PI(s) and study site
- Confirm the facility(-ies) are satisfactory to continue study conduct
- Confirm the site is adhering to the protocol, data are being accurately recorded in the eCRFs, and IP accountability checks are being performed
- Confirm that the study site staff are routinely reviewing the participants e-diary records
- Perform source data verification including a comparison of eCRF data with the participant's clinic records and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinic charts)
- Record and report any protocol deviations not previously sent to Emergent
- Confirm AEs, AESIs, and SAEs have been properly documented on eCRFs; SAE, AESI, and pregnancy reports where conception occurred after first exposure to the IP and (ie, after receipt of at least one dose of either IP), and prior to 12 months after last receipt of either IP have been sent to Emergent; and SAEs and potential AESIs meeting the criteria for reporting have been sent to the IRB/IEC
- Confirm all pregnancies where conception occurred after first exposure to the IP (ie, after receipt of at least one dose of either IP), and prior to 12 months after receipt of either IP are followed properly and that the post-birth follow-up occurs

The CRO study monitors may inspect all documents and required records that are maintained by the PI, including medical records (office, clinic, or hospital) for the participants in this trial. The PIs will permit unrestricted access to all source documents. Source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of AEs, accuracy of data collected on eCRFs, and device procedure information. A monitoring visit sign-in log will be maintained at the site. The PI and investigational site staff will be available for monitoring visits. It is expected that the PI will

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provide the CRO study monitors with a suitable working environment for review of study-related documents and internet access.

12.2. Auditing

Emergent's Quality Assurance Department (or designee[s]) may conduct investigational site audits before trial initiation, during the trial, or after trial completion, as documented in the Clinical Quality Oversight Plan. Audits will include, but are not limited to, review of drug supply, presence of required documents, informed consent process, and comparison of eCRFs with source documents. The PI agrees to participate in site audits and assist in the prompt resolution of any issues found during audits.

Regulatory authorities or the IRB/IEC may inspect the investigational site during or after the trial. The PI will cooperate with such inspections and will contact Emergent immediately if such an inspection occurs.

In the event the PI is contacted by a regulatory agency in relation to this study, the PI and investigational site staff must be available to respond to reasonable requests and inspection queries made during the inspection process. The PI must provide Emergent with copies of all correspondence that may affect the review of the current study (eg, Form FDA 483, inspectional observations, warning letters). Emergent may provide any needed assistance in responding to regulatory inspections.

[redacted]

13. ETHICS

This trial must be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol, ICH E6 GCP Guideline, FDA regulations, and all other applicable local laws and regulatory requirements. Each investigational site will seek approval by an IRB/IEC according to regional requirements. The IRB/IEC will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in collecting and handling participant data and completing eCRFs, the PI and investigational site staff will take measures to ensure adequate care in protecting participant privacy. To this end, a subject ID number will be used to identify each participant.

13.1. Informed Consent

The Principal Investigator (PI) or designee at each site will ensure the participant is given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the trial. Written informed consent will be obtained from all participants and documented on a written ICF. The ICF will be approved by the same institutional review board/ independent ethics committee (IRB/IEC) that approves this protocol. Each ICF will comply with the FDA regulations in 21 CFR Part 50, ICH guidelines and local regulatory requirements.

Investigators may discuss trial availability and the possibility for entry with a potential participant without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial.

Once appropriate essential information has been provided and fully explained in layman's language to the participant by the PI or a qualified designee (and source documented at the site), the IRB/IEC approved written ICF will be signed and dated by both the participant and the person obtaining consent (PI or designee), as well as by any other parties required by the IRB/IEC. The participant will receive a copy of the signed/dated ICF; the original shall be kept on file by the PI.

13.2. Institutional Review Board

The final study protocol, associated ICF, and any recruitment materials must be reviewed and approved by the IRB/IEC at each investigational site. The potential benefits and risks for participants will be considered as will the benefits to the knowledge gained through the conduct of the proposed study. The PI or designee must submit written approval from the IRB/IEC to Emergent before any participants can be screened for the study.

The PI or designee is responsible for informing the IRB/IEC of any amendment to the protocol or ICF in accordance with local requirements. The protocol must be re-approved by the IRB/IEC upon receipt of amendments and annually, as required by local regulations.

The PI or designee is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the IP, if required by the IRB/IEC. Emergent will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines, if required.

Additionally, the PI or designee will provide an IRB/IEC membership list or assurance number to Emergent annually. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for the study including the ICF and recruitment materials, must be maintained by the PI and made available for inspection.

13.3. Future Use of Stored Specimens

Any remnant (leftover) blood samples collected for the TNA analysis will be stored frozen at a long-term storage facility for possible later retesting for anthrax research. Specimens will be identified by subject ID numbers, thereby maintaining confidentiality while in storage. Participants will be asked to consent to the future use of these samples as part of the informed consent process.

Samples may be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the vaccine. They may be retained for a longer period, however, if required by the applicable regulatory requirements.

13.4. Confidentiality

Participant confidentiality must be strictly held in trust by the participating PIs, their staff, and Emergent and its agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Participants will be identified only by their subject ID or other de-identifying information, on the eCRF or any other study documents provided to Emergent or designate(s).

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of Emergent.

[redacted]

14. AMENDMENT POLICY

The PI will not make any changes to this protocol. Any permanent change to the protocol, whether it be an overall change or a change for specific investigational site(s), must be handled as a protocol amendment. Any amendment will be initiated/written by Emergent. Each amendment will be submitted to the IRB/IEC. Except for non-substantial, in other words, administrative, amendments, PIs will wait for IRB/IEC approval of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety or physical or mental integrity of participants, the conduct or management of the trial, the scientific value of the trial or the quality or safety of IP(s) used in the trial. However, a protocol change intended to eliminate an apparent immediate hazard to participants should be implemented immediately, followed by IRB/IEC notification within 5 working days. Emergent will submit protocol amendments to the FDA or other regulatory agencies.

When the IRB/IEC, PIs, and/or Emergent conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the participant, the currently approved written ICF will require similar modification. In such cases, after approval of the new ICF by the IRB/IEC, repeat informed consent will be obtained from participants in a timely manner before expecting continued participation in the trial.

[redacted]

15. PUBLICATION POLICY

Following the completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, Emergent will be responsible for these activities and may work with the PI(s) to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted and other related issues. Emergent has final approval authority over all such issues.

Any proposed publication will be subject to review conditions and timelines agreed between Emergent and the site PI and detailed in the agreements with these parties prior to the start of the study. Emergent will also post the results of the clinical trial on ClinicalTrial.gov in a period no greater than 12 months from the completion of the study, defined as the time the final participant was examined or received an intervention for purposes of final collection of data for one of the primary endpoints.

Data are the property of Emergent and cannot be published without prior authorization from Emergent, but data and publication thereof will not be unduly withheld.

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17. APPENDICES

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APPENDIX A. TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

The toxicity grading scales that will be used to rate the severity of local reaction to injectable product, vital signs, and general systemic condition related to clinical abnormality and laboratory abnormality are presented in Table 12 and Table 13, respectively.

Table 12: Toxicity Grading Scale for Clinical Abnormalities in Healthy Adult and Adolescent Volunteers

Toxicity	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potential Life-Threatening)
Local Reaction to Injectable Product				
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/redness[a]	2.5–5 cm	5.1–10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/swelling[b]	2.5–5 cm and does not interfere with activity	5.1–10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
Vital Signs[c]				
Fever (°C) (°F)[d]	38.0–38.4 100.4–101.1	38.5–38.9 101.2–102.0	39.0–40 102.1–104	>40 >104
Tachycardia (beats/minute)	101–115	116–130	>130	ER visit or hospitalization for arrhythmia
Bradycardia[e] (beats/min)	50–54	45–49	<45	ER visit or hospitalization for arrhythmia
Hypertension – systolic (mmHg)	141–150	151–155	>155	ER visit or hospitalization for malignant hypertension
Hypertension – diastolic (mmHg)	91–95	96–100	>100	ER visit or hospitalization for malignant hypertension
Hypotension – systolic (mmHg)	85–89	80–84	<80	ER visit or hospitalization for hypotensive shock

[redacted]

Toxicity	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potential Life-Threatening)
Respiratory rate (breaths/minute)	17–20	21–25	>25	Intubation
Systemic (General)				
Nausea/vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2–3 loose stools or <400 g/24 hours	4–5 stools or 400–800 g/24 hours	≥ 6 watery stools or >800 g/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Illness or clinical AE[f]	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

AE = adverse event; ER = emergency room; gm = grams; IV = intravenous
[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement is recorded as a continuous variable.
[b] Induration/swelling is evaluated and graded using the functional scale as well as the actual measurement.
[c] Participant will be at rest for all vital sign measurements.
[d] Oral temperature; no recent hot or cold beverages or smoking.
[e] When resting heart rate is between 60-100 beats per minuteclinical judgment will be used when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.
[f] Adverse event defined according to applicable regulations.

[redacted]

Table 13: Toxicity Grading of Laboratory Abnormalities

Panel and Analyte[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)[b]
Serum Chemistry				
Glucose – hypoglycemia mg/dL	65–69	55–64	45–54	< 45
Glucose – hyperglycemia Fasting (mg/dL) Random (mg/dL)	 100–110 110–125	 111–125 126–200	 >125 >200	 Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen (mg/dL) – mg/dL	23–26	27–31	> 31	Requires dialysis
Creatinine (mg/dL)	1.5–1.7	1.8–2.0	2.1–2.5	> 2.5 or requires dialysis
Alkaline phosphate increase by factor	1.1–2.0 x ULN	2.1–3.0 x ULN	3.1–10 x ULN	> 10 x ULN
Liver Function Tests: ALT, AST increase by factor	1.1–2.5 x ULN	2.6–5.0 x ULN	5.1–10 x ULN	> 10 x ULN
Bilirubin (when accompanied by any increase in Liver Function Test) increase by factor	1.1–1.25 x ULN	1.26–1.5 x ULN	1.51–1.75 x ULN	> 1.75 x ULN
Bilirubin (when Liver Function Test is normal) increase by factor	1.1–1.5 x ULN	1.6–2.0 x ULN	2.0–3.0 x ULN	> 3.0 x ULN
Hematology				
Hemoglobin, female (g/dL)	11.0–12.0	9.5–10.9	8.0–9.4	<8.0
Hemoglobin decrease from baseline value, female (g/dL)	Any decrease–1.5	1.6–2.0	2.1–5.0	>5.0
Hemoglobin, male (g/dL)	12.5–13.5	10.5–12.4	8.5–10.4	<8.5
Hemoglobin decrease from baseline value, male (g/dL)	Any decrease–1.5	1.6–2.0	2.1–5.0	>5.0

[redacted]

Panel and Analyte[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)[b]
WBC increase (cell/mm^3)	10,800–15,000	15,001–20,000	20,001–25,000	>25,000
WBC decrease (cell/mm^3)	2,500–3,500	1,500–2,499	1,000–1,499	<1,000
Lymphocyte decrease (cell/mm^3)	750–1,000	500–749	250–499	<250
Neutrophil decrease (cell/mm^3)	1,500–2,000	1,000–1,499	500–999	<500
Eosinophils (cell/mm^3)	650–1,500	1,501–5,000	>5,000	Hypereosinophilic
Platelets decrease (cell/mm^3)	125,000–140,000	100,000–124,000	25,000–99,000	<25,000
Urine				
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) (RBC/hpf)	1–10	11–50	>50 and/or gross blood	Hospitalization or PRBC transfusion

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HPF = high power field); PRBC = packed red blood cells; RBC = red blood cells; ULN = upper limit of normal range; WBC = white blood cell.

[a] Laboratory normal reference ranges have not been taken into consideration for the toxicity grading scale.

[b] The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) will be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

[redacted]

APPENDIX B. ADVERSE EVENTS OF SPECIAL INTEREST

Note: These listed AEs (Version 3, provided to Emergent by CBER on 24 October 2017), may indicate diseases with autoimmune etiology and will be immediately reported to Emergent.

Table 14: List of Adverse Events of Special Interest*

Gastrointestinal Disorders
• Celiac disease • Crohn's disease • Ulcerative colitis • Ulcerative proctitis
Liver Disorders
• Autoimmune cholangitis • Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis
Metabolic Diseases
• Addison's disease • Autoimmune thyroiditis (including Hashimoto thyroiditis) • Diabetes mellitus type I • Graves' or Basedow's disease
Musculoskeletal Disorders
• Antisynthetase syndrome • Dermatomyositis • Juvenile chronic arthritis (including Still's disease) • Mixed connective tissue disorder • Polymyalgia rheumatic • Polymyositis • Psoriatic arthropathy • Relapsing polychondritis • Rheumatoid arthritis • Scleroderma, including diffuse systemic form and CREST syndrome • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Systemic lupus erythematosus • Systemic sclerosis
Neuroinflammatory Disorders
• Acute disseminated encephalomyelitis, including site specific variants (eg, non-infectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis) • Cranial nerve disorders, including paralyses/paresis (eg, Bell's palsy) • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy • Multiple sclerosis • Narcolepsy • Optic neuritis • Transverse Myelitis • Myasthenia gravis, including Eaton-Lambert syndrome

[redacted]

Skin Disorders
• Alopecia areata • Autoimmune bullous skin diseases, including pemphigus, pemphigoid and dermatitis herpetiformis • Cutaneous lupus erythematosus • Erythema nodosum • Erythema multiforme • Morphoea • Lichen planus • Psoriasis • Rosacea • Sweet's syndrome • Vitiligo
Vasculitides
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease thromboangiitis obliterans, necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch- Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis
Others
• Antiphospholipid syndrome • Autoimmune hemolytic anemia • Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Autoimmune myocarditis/cardiomyopathy • Autoimmune thrombocytopenia • Goodpasture syndrome • Idiopathic pulmonary fibrosis • Pernicious anemia • Raynaud's phenomenon • Sarcoidosis • Sjögren's syndrome • Stevens-Johnson syndrome • Uveitis

*Emergent added erythema multiforme.

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APPENDIX C. SPONSOR'S GUIDANCE ON CHRONIC CONDITIONS FOR INVESTIGATORS

The Sponsor's guidance on the interpretation of stability or seriousness of chronic conditions for study eligibility purposes is outlined below.

A chronic illness is NOT exclusionary IF the following three conditions are met:

- The condition is not serious (no history of ER visit, hospitalization, or other urgent medical intervention for the condition)
- The condition is stable (no clinical or medication changes in the last six months)
- The condition does not require treatment with any prohibited medication (protocol Section 6.5, Table 3) or medication that would appear on the urine drug screen.

This guidance would apply to conditions such as:

- Insomnia
- Migraine
- Seasonal allergy
- Asthma
- Gastroesophageal reflux disease (GERD)
- Anxiety
- Attention-deficit/hyperactivity disorder (ADHD)
- Depression
- Scoliosis
- Fibromyalgia
- Osteoarthritis (NOT rheumatoid arthritis or reactive arthritis, which are AESIs as per Appendix B of the protocol)

Specifically, for Type 2 diabetes mellitus (DM) and hypercholesterolemia:

- The condition is not serious (no history of ER visit, hospitalization, or other urgent medical intervention for the condition)
- The condition is stable (no clinical or medication changes in the last six months) AND is within relevant treatment guidelines
  - For Type 2 DM: Standards of Medical Care in Diabetes – 2019
  - For hypercholesterolemia: American College of Cardiology/American Heart Association (AHA/ACC) Guideline on the Management of Blood Cholesterol – 2018
- The condition, if treated, requires only a single agent that is not a prohibited medication (Section 6.5, Table 3) or medication that would appear on the urine drug screen.

Please note that Exclusion criterion #22 states that a serious chronic illness is exclusionary (not just cancer/malignancies).

[redacted]

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