A Phase 3, Randomized, Double-blind, Parallel-group Trial to Evaluate the Lot Consistency, Immunogenicity, and Safety of AV7909 for Postexposure Prophylaxis of Anthrax in Healthy Adults

Clinical Protocol EBS.AVA.212

Version 4.2

14-March-2019

Sponsor: [redacted]

CONFIDENTIAL

KEY STUDY CONTACT INFORMATION

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SPONSOR'S SIGNATURE PAGE

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[redacted] Date

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. federal regulations and International Council on 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/international 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

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Table 1: Abbreviations

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
AESI	Adverse event of special interest
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibodies
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AVA	Anthrax vaccine adsorbed
AVA_{max}	Maximum TNA concentration for subjects in the AVA-alone arm
BARDA	Biomedical Advanced Research and Development Authority
BUN	Blood urea nitrogen
CBC	Complete blood count
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control & Prevention
CFR	Code of Federal Regulations
CI	Confidence interval
CpG ODNs	Synthetic oligonucleotides that contain a cytosine triphosphate deoxynucleotide ("C") followed by a guanine triphosphate deoxynucleotide ("G")
CPK	Creatine phosphokinase
CRO	Contract research organization
DMP	Data Management Plan
(ds)DNA	(double-stranded) Deoxyribonucleic acid
DSMB	Data safety monitoring board
eCRF	Electronic case report form
ED_{50}	50% effective dilution
EDC	Electronic data capture
e-diary	Electronic diary
EF	Edema factor
ER	Emergency room

Abbreviation	Definition
EWV	Early withdrawal visit
FDA	Food and Drug Administration
FSFV	First subject, first visit
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM(T)	Geometric mean (titer)
GP	Guinea pig
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPF	High power field
ID	Identification
ICF	Informed consent form
ICH	International Council/Conference on Harmonisation
IEC	Independent ethics committee
IM	Intramuscular
IND	Investigational New Drug (application)
IP	Investigational product
IRB	Institutional review board
ISO	International Organization for Standardization
ITT	Intent to treat
IUD	Intrauterine device
IV	Intravenous
IxRS	Interactive voice and/or web response system
LB	Lower bound
LD_{50}	50% lethal dose
LF	Lethal factor
LLOQ	Lower limit of quantification
LOD	Limit of detection
LSLV	Last subject, last visit
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical monitor

Abbreviation	Definition
NA	Not applicable
NF_{50}	50% neutralization factor
NHP	Nonhuman primate
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drugs
ODN	Oligodeoxynucleotide
PA	Protective antigen
PE	Physical examination
PEP	Postexposure prophylaxis
PI	Principal investigator
PP	Per protocol
PRBC	Packed red blood cells
PT	Preferred term (MedDRA)
PV	Pharmacovigilance
RBC	Red blood cell
RF	Rheumatoid factor
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class (MedDRA)
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TNA	Toxin neutralizing antibody
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States of America
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

1. SYNOPSIS

Name of Sponsor/Company: Emergent Product Development Gaithersburg, Inc. (Emergent)

Name of Investigational Product: AV7909

Name of Active Ingredient(s): AVA bulk drug substance and CPG 7909 adjuvant

Title of Study: A Phase 3, Randomized, Double-blind, Parallel-group Trial to Evaluate the Lot Consistency, Immunogenicity, and Safety of AV7909 for Postexposure Prophylaxis of Anthrax in Healthy Adults

Study center(s): Approximately 40 sites in the United States (US)

Studied Period (months):

Individual participation in the study from the participant's first visit to last visit inclusive of safety follow up will be approximately 15 months. Screening will be from Day -28 to Day -2 followed by four in-clinic visits occurring over 9 weeks. Safety follow-up phone calls will be conducted at Day 43 and Months 4, 7, 10, and 13 (nominally 0.5, 3, 6, 9, and 12 months after the last vaccination).

Overall study duration from the first subject first visit (FSFV) to last subject last visit (LSLV) is anticipated to be approximately 20 months.

Phase of Development: Phase 3

Objectives:

Primary:

- To demonstrate lot consistency following a two-dose schedule of AV7909 (Days 1 and 15) administered intramuscularly (IM) in healthy adults
- To demonstrate immunogenicity under the US Food and Drug Administration's (FDA's) Animal Rule on Day 64 following a two-dose schedule of AV7909 (Days 1 and 15) administered IM in healthy adults
- To demonstrate immunogenicity using the US FDA's Animal Rule at Day 64 based on the noninferiority of a two-dose schedule of AV7909 (Days 1 and 15) administered IM to the licensed three-dose schedule of BioThrax® (Days 1, 15, and 29) administered subcutaneously (SC) in healthy adults
- To evaluate the safety of AV7909 in healthy adults following a two-dose schedule (Days 1 and 15) administered IM

Secondary:

- To demonstrate immunogenicity under the US FDA's Animal Rule on Day 29 following a two-dose schedule of AV7909 (Days 1 and 15) administered IM in healthy adults

Study Design:

This is a phase 3, multicenter, randomized, double-blind, parallel-group trial designed to evaluate the lot consistency (using three consecutive lots), immunogenicity, and safety of a two-dose schedule of AV7909 (Days 1 and 15) administered IM in healthy adults for an indication of postexposure prophylaxis (PEP) of anthrax.

Healthy adults between 18 and 65 years of age (inclusive) will sign and date an informed consent form and then be screened for eligibility for participation in the study 2 to 28 days prior to randomization. Participants meeting the entry criteria will be randomized 2:2:2:1 (block size of 7) to one of four study groups on Day 1, as shown in the table below. Randomization will be stratified by site. Racial distribution will be monitored among recruited participants. Participants who are randomized and do not receive vaccination on the same day will be withdrawn from the study.

Study Groups

Group Number	Sample Size	Day 1	Day 15	Day 29
1	1100	AV7909 Lot 1 (IM)	AV7909 Lot 1 (IM)	Placebo (SC)
2	1100	AV7909 Lot 2 (IM)	AV7909 Lot 2 (IM)	Placebo (SC)
3	1100	AV7909 Lot 3 (IM)	AV7909 Lot 3 (IM)	Placebo (SC)
4	550	BioThrax (SC)	Biothrax (SC)	BioThrax (SC)
Total	3850			

IM = intramuscular injection in the deltoid muscle; SC = subcutaneous injection over the deltoid region.

Blood samples for immunogenicity testing will be collected prior to vaccination on Day 1 (baseline) and on Days 29 and 64 and assayed using toxin neutralization assay. The assay results will be reported as the reciprocal of a serum sample dilution that results in 50% neutralization of cytotoxicity of the lethal toxin (50% effective dilution; ED_{50}). To standardize assay results, the results will be divided by the ED_{50} of a serum reference standard, and the resulting ratio will be reported as a 50% neutralization factor (NF_{50}).

Participants will be evaluated for safety through Day 64 (or the early withdrawal visit [EWV]), as assessed by clinical laboratory tests (hematology, serum chemistry, and urinalysis), monitoring of adverse events (AEs) including serious adverse events (SAEs) and adverse events of special interest (AESIs), vital signs, and physical examinations (PEs). Adverse events of special interest are AEs associated with autoimmune disease as defined by the Center for Biologics Evaluation and Research [CBER]), and might 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 Preventative Vaccine Clinical Trials*. Reactogenicity (solicited systemic and injection site reactions) will be assessed daily by the participants using e-diaries for at least seven days after each vaccination. If injection site or systemic reactions continue beyond seven days, participants will be prompted to continue e-diary entries until resolved for at least two consecutive days. Use of medications will be collected at each study visit. In addition, blood samples for auto-antibody assessment will be taken at Day 1 predose and Day 64 (or EWV) for testing for rheumatoid factor (RF), antinuclear antibody (ANA) and anti-double stranded deoxyribonucleic acid (dsDNA) antibodies, as well as for thyroid-stimulating hormone (TSH) assessment. To ensure a robust safety follow up, participants who receive at least one dose of vaccine but for any reason discontinue vaccinations prematurely will be asked to participate in the further planned study visits up to Day 64 for safety assessment only.

Participants who receive at least one dose of vaccine will also participate in safety follow-up phone calls occurring on Day 43, Month 4, Month 7, Month 10, and Month 13 (nominally 0.5, 3, 6, 9, and 12 months after the last vaccination) to collect information on SAEs and any potential AESIs. Based on responses at these phone contacts, participants may be asked to return to the clinic for an unscheduled visit to provide blood samples for auto-antibody testing to investigate potential AESI(s).

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 eCRF, potential AESIs of autoimmune etiology, or any other events the medical monitor deems medically relevant) 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. A planned interim DSMB safety data review will be conducted after the first 500 participants have completed the Day 29 visit, comprising all safety evaluations through two weeks after the second vaccination. All DSMB reviews will be performed with blinded data, unless otherwise requested by the DSMB Chair. 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.

Number of Subjects (Planned): 3850

Diagnosis and Main Criteria for Study Participation:

Healthy males and females aged 18 to 65 years (inclusive) with no prior history of anthrax disease, suspected exposure to anthrax, or vaccination with anthrax vaccine as determined by inclusion and exclusion criteria listed below.

Inclusion Criteria

1. Written informed consent obtained from the participant (dated and signed).
2. Healthy condition as established by medical history and clinical examination before entering into the study.
3. A male or female aged 18 to 65 years, inclusive, at the time of informed consent.
4. Body mass index (BMI) $\leq$35.0 kg/m^2 at Screening visit.
5. Have adequate venous access for phlebotomies.
6. For a woman of childbearing potential (WOCBP), negative serum pregnancy test at Screening and negative urine pregnancy test prevaccination on Day 1, not currently breastfeeding, and no intention to become pregnant during the study through Month 13.

   Every female participant is considered to be a WOCBP unless surgically sterile (bilateral oophorectomy or bilateral salpingectomy or hysterectomy) OR postmenopausal (defined as >12 consecutive months without menses and screening follicle-stimulating hormone [FSH] >30 mIU/mL). Women who are not of childbearing potential are allowed to enroll if they are surgically sterile or postmenopausal as defined above.

Exclusion Criteria

1. Use of any investigational or nonregistered product (drug, vaccine, device, or combination product) within 30 days preceding the dose of study vaccine, or planned use during the study through Month 13.
2. Positive test 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.
3. Chronic administration (defined as >14 days) of immunosuppressants or other immune-modifying drugs (includes oral or parenteral corticosteroids, eg, a glucocorticoid dose exceeding 10 mg/day prednisone or equivalent) within six months prior to the vaccine dose; inhalation use (eg, for seasonal allergies) is permitted.
4. Planned administration of any commercially-available vaccine from seven days prior to the first study vaccination through two weeks after the last vaccination.

5. 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), or latex.
6. History of anthrax disease, suspected exposure to anthrax, or previous vaccination with any anthrax vaccine.
7. Have a tattoo/scar/birthmark or any other skin condition affecting the deltoid area that may interfere with injection site assessments.
8. A positive blood test for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) HIV-1 or HIV-2 antibodies.
9. Any confirmed or suspected immunodeficiency condition (congenital or secondary) or autoimmune disease based on medical history and PE, eg, Guillain-Barré.
10. A family history of congenital or hereditary immunodeficiency.
11. Major congenital defects or serious chronic illness, including any cancer other than the following: a) any non-metastatic cancer (excluding hematologic malignancies) or melanoma of which the participant has been disease-free for at least five years and b) localized skin cancer, resected (including squamous cell and basal cell carcinomas).
12. 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.
13. Any medical condition that, in the opinion of the investigator, could adversely impact the participant's participation or the conduct of the study.
14. Any planned elective surgery during the study through 12 months after the last vaccination.
15. Planned 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 phone contact.
16. Woman of childbearing potential refusing to practice an adequate method of contraception from at least one month before Day 1 and continuing through Month 13.

    An adequate method of contraception is defined as abstinence from sexual intercourse; prior bilateral tubal ligation; monogamous relationship with a vasectomized partner (vasectomy performed at least six months prior to the participant's screening visit); or any of these forms of birth control: pill, intrauterine device (IUD), implantable or injectable contraceptive (eg, Norplant® or Depo-Provera®), removable device (eg, NuvaRing® or Evra® patch), or double-barrier method (condom with spermicide, diaphragm with spermicide). The PI

and/or designee will discuss with the participant the need to use adequate contraception consistently and correctly and document such conversation in the participant's chart. In addition, the PI and/or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

17. Member or family member of the investigator site team.
18. Previously served in the military any time after 1990 and/or plan to enlist in the military at any time from screening through the final telephone contact.

Investigational Product (IP), Dosage and Mode of Administration:

AV7909: Three consecutive lots of AV7909 vaccine (containing 0.5 mL AVA + 0.25 mg CPG 7909 adjuvant per dose) are to be administered IM on Days 1 and 15 in Groups 1 to 3, respectively.

Placebo (saline for injection): Saline for injection will be administered SC on Day 29 in Groups 1 to 3 to mask the vaccine schedule.

Duration of Treatment:

Three vaccinations will be administered two weeks apart.

Reference Therapy, Dosage and Mode of Administration:

BioThrax (Anthrax Vaccine Adsorbed [AVA]): In Group 4, one lot of BioThrax (containing 0.5 mL AVA per dose) is to be administered subcutaneously (SC) on Days 1, 15, and 29.

Criteria for Evaluation:

Primary:

Lot Consistency:

- Equivalent immunogenicity across three consecutive AV7909 lots as demonstrated by the 95% confidence interval (CI) for the ratios of geometric mean TNA NF_{50} at Day 64 for each of the three lot-to-lot comparisons to be within 0.5 and 2.0.
- Protective level of immunogenicity in all three consecutive AV7909 lots as demonstrated by the lower bound (LB) of the two-sided 95% CI to be ≥40% for the proportions of AV7909 subjects in each of the three lots achieving a TNA NF_{50} ≥0.56 at Day 64. For this endpoint, the threshold of protection (0.56) is based on the Day 70 TNA NF_{50} value associated with 70% survival in rabbits administered BioThrax on Days 0 and 28 and challenged on Day 70 with *Bacillus anthracis* spores (Study 646).

Immunogenicity:

- Lower bound of the two-sided 95% CI is ≥40% for the proportion of AV7909 participants in Groups 1-3 (three lots pooled) achieving a TNA NF_{50} ≥0.56 on Day 64.
- Non-inferiority of AV7909 to BioThrax at Day 64 as determined by the two-sided lower 95% CI of the difference in the proportion of AV7909 participants (three lots pooled) with a TNA NF_{50} ≥0.29 and the proportion of BioThrax participants with a TNA NF_{50} value ≥0.29 being greater than -15%. For this endpoint, the threshold of protection (0.29) is based on the Day 70 TNA NF_{50} value associated with 70% survival in nonhuman primates (NHPs) administered BioThrax on Days 0 and 28 and challenged on Day 70 (Study 844).

Safety:

- Incidences of SAEs from the time of the first vaccination on Day 1 through the 12-month safety follow-up telephone call following the last vaccination.

Secondary:

Immunogenicity:

- Lower bound of the two-sided 95% CI will be ≥67% for the proportion of AV7909 participants in Groups 1-3 (three lots pooled) achieving a TNA NF_{50} ≥0.15 on Day 29. For this endpoint, the threshold of protection (0.15) is based on the Day 28 TNA NF_{50} value associated with 70% survival in NHPs administered AV7909 on Days 0 and 14 and challenged on Day 28 (Study 3655).

Safety:

- Incidences of AEs from the time of the first vaccination on Day 1 through Day 64.
- Incidences of clinical laboratory abnormalities.
- Incidences of autoimmune-associated AESIs from the time of the first vaccination on Day 1 through the 12-month safety follow-up telephone call following the last vaccination.
- Incidences of solicited systemic reactions and solicited injection site reactions by severity following each vaccination as reported in participant e-diaries.

Statistical Methods:

Analysis Populations:

The Intent-to-treat (ITT) Population will include all randomized participants.

The Safety Population will include all randomized participants who receive at least one vaccination. Safety analyses will be based on the Safety Population according to the vaccine received (BioThrax and combined AV7909 groups).

The Per Protocol (PP) Population used for analyses of immunogenicity will include participants who are randomized and do not have any of the deviations listed below:

- History of previous anthrax disease, anthrax exposure, or anthrax vaccination as per eligibility criteria, as evidenced by a baseline (Day 1 prevaccination) TNA NF_{50} above the limit of detection
- Missing or out of window vaccination visit at Study Day 15
- Missing or out of window vaccination visit at Study Day 29 for the BioThrax group
- Administration issue(s) with IP, eg, the incorrect dose of IP at one or more vaccination visits, administration of IP associated with a temperature excursion
- Use of prohibited or restricted medications which may have impacted immune response to vaccination as assessed by the Sponsor (this assessment will be completed prior to database lock)
- Missing immunogenicity data (eg, sample out-of-window, sample not shipped/received, sample not usable by the immunogenicity lab, sample associated with loss of cold chain) at Day 64

Sample Size Considerations:

Sample size for this study is based primarily on safety considerations. The total sample size across all three AV7909 groups is set at 3300 participants. Allowing a 10% drop-out rate, this sample size for safety (3000) is sufficient to detect, with 95% probability, an AE rate of 1:1000, or 0.1%.

It is expected that more participants will be excluded from the PP Population than excluded from the Safety Population. A 25% exclusion rate from the PP Population is assumed. Thus, the PP Population will be approximately 800 participants for each AV7909 group (2400 participants total) and 400 participants for the BioThrax group.

Even under the best manufacturing practices, between-lot variation exists and will be considered normal. It is assumed that the lot-to-lot geometric mean titer (GMT) ratio could be as low as 0.6 based on Emergent's experience with the BioThrax vaccine. Conservatively, the largest GMT ratio between two out of three lots is assumed to be 1.5. Assuming a coefficient of variation of 100% (slightly larger than the observed 91% in the phase 2 study, EBS.AVA.208), this study has >99% power to demonstrate lot consistency with the pre-specified equivalence bounds ([0.5, 2.0]) in terms of GMT ratio for TNA NF_{50} at Day 64.

Based on the combined phase 1 and phase 2 data, the proportion of subjects receiving two doses of AV7909 on Day 1 and Day 15 with TNA NF_{50} at Day 64 over 0.56 is approximately 63% with lower 95% CI of 50% (total n = 54). Even assuming a

conservative 50%, the study provides >99% power of rejecting the null hypothesis of 40% in each of the three AV7909 lots and in the combined AV7909 group (three lots pooled).

For the non-inferiority endpoint, among subjects (n = 184) receiving BioThrax PEP regimen (3 doses, SC) in the EBS.AVA.006 study, 93.5% had TNA NF_{50} values above 0.29 at Day 64. In the AV7909 phase 2 study (EBS.AVA.208), 86.5% of subjects (n = 37) had TNA NF_{50} above 0.29 at Day 64. Assuming a rate of 93% for the BioThrax group and 83% for the AV7909 group, the sample sizes of 400 and 2400 provide approximately 98% power to demonstrate non-inferiority of the two-dose AV7909 IM regimen to the three-dose BioThrax SC regimen at Day 64 with a non-inferiority margin of 15%.

Considerations for Multiple Endpoints:

Primary Endpoints (Lot Consistency and Immunogenicity):

The primary endpoints assessed using immunogenicity data will be tested in the hierarchy below. Testing of the next endpoint will only be carried out when all previous endpoints are met. According to the closed testing principle, this procedure ensures that the overall type I error rate is controlled at less than 5% and no additional adjustment is needed.

1a. AV7909 Lot Consistency Based on GMT Ratio of TNA NF_{50} at Day 64: the 95% CIs for the Day 64 TNA NF_{50} geometric mean ratios between all three pairs of AV7909 groups (Lot 1 vs. Lot 2, Lot 2 vs. Lot 3, and Lot 1 vs. Lot 3) are within 0.5 and 2.0.

1b. AV7909 Lot Consistency Based on Protective Level of Immunogenicity at Day 64: protective level of immunogenicity in all three consecutive AV7909 lots as demonstrated by the LB of the two-sided 95% CI to be ≥40% for the proportions of AV7909 participants in each of the three lots achieving a TNA NF_{50} ≥0.56 at Day 64.

The two endpoints 1a and 1b must both be met to demonstrate AV7909 lot consistency.

2a. AV7909 Immunogenicity at Day 64: once lot consistency is demonstrated, the immunogenicity data on Day 64 will be pooled across all three AV7909 lots. AV7909 will be considered as achieving a protective level of immunity under the US FDA's Animal Rule at Day 64 if the LB for the two-sided 95% CI for the proportion of participants with TNA NF_{50} values above the specified threshold of protection (≥0.56) is ≥40%.

2b. AV7909 Immunogenicity Based on Non-inferiority vs BioThrax at Day 64: the difference in the proportion of participants with TNA NF_{50} values above the specified threshold of protection (≥0.29) will be calculated using the pooled AV7909 groups versus the BioThrax group. Non-inferiority is demonstrated if the two-sided 95% lower CI of difference in proportions (AV7909 - BioThrax) is above -15%.

Secondary Endpoint (Immunogenicity):

AV7909 will be considered appropriately immunogenic under the US FDA's Animal Rule on Day 29 if the LB for the 95% CI for the proportion of participants pooled from all three

AV7909 groups with TNA NF_{50} values above the specified threshold of protection (≥0.15) is ≥67%. (Note: The primary lot consistency and immunogenicity endpoints must all be met for testing to proceed to the secondary immunogenicity endpoint.)

Safety:

Adverse events will be coded to a system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (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 summary categories of TEAEs (eg, any TEAEs, any drug-related TEAEs, any Grade 3 or 4 TEAEs) and using the MedDRA coded terms of SOC and PT overall, by ≥2% incidence in either group, and by severity (toxicity grade), seriousness, relationship to IP, and outcome (death, discontinuation of IP, study withdrawal) for each study group. A separate tabulation will be provided of treatment-emergent AESIs determined to be of autoimmune etiology based on decision of the DSMB. Relative risk and 95% CIs will be provided for the incidences of serious TEAEs and treatment-emergent AESIs between the pooled AV7909 group and BioThrax group.

Medications will be coded according to the World Health Organization's (WHO) WHODrug Global Dictionary and daily dosages normalized. Laboratory values and other safety evaluations (eg, vital signs, medication use, participant e-diary) will be presented for each study group as summary statistics, and also by reporting any clinically significant values for individuals.

2. INTRODUCTION

2.1. Study Rationale

This is intended as the licensure-enabling study of AV7909 for the indication of postexposure prophylaxis (PEP) of disease resulting from suspected or confirmed *Bacillus anthracis* exposure, when combined with the recommended course of antimicrobial therapy in persons 18 through 65 years of age inclusive. AV7909 consists of AVA bulk drug substance and CPG 7909 adjuvant. AVA drug substance is identical in composition and manufacturing process to commercial BioThrax® (Anthrax Vaccine Adsorbed; AVA), which was licensed in November 2015 for anthrax PEP as a three-dose vaccine series administered subcutaneously (SC) two weeks apart (weeks 0, 2, and 4) given with 60 days of antimicrobial therapy. BioThrax received its initial licensure in 1970 for pre-exposure prophylaxis of anthrax disease in persons at high risk of exposure. CPG 7909 is an immunostimulatory synthetic oligodeoxynucleotide containing unmethylated CG (cytosine – guanine) dinucleotides (CpG ODN) that functions as an adjuvant by activation of the Toll-like receptor 9 (TLR9). CPG 7909 is designed to induce both an enhanced antigen-specific antibody response and a natural killer T-cell response when used in combination with prophylactic or therapeutic vaccines {Krieg et al, 1996; Pittman et al, 2002; Pisetsky et al, 1996; Kim et al, 1999}. CPG 7909 is not currently approved in any region as monotherapy or combination use for any indication. CpG-containing Heplisav-B® (hepatitis B vaccine with adjuvant CpG 1018; Dynavax Technologies Corporation) received FDA licensure in 2017.

The goal of the AV7909 product development program has been to develop a new vaccine that will accelerate the immune response, reduce the number of injections needed to induce full protection, and possibly reduce the amount of antigen per injection needed to achieve protection. Based on the available preliminary data, AV7909 would have the following advantages over BioThrax for anthrax PEP, as follows:

- more convenient dosing schedule of two (instead of three) vaccinations administered two weeks apart (on Days 1 and 15).
- protective antibody response induced approximately three weeks earlier {Rynkiewicz et al, 2011}. Delayed protection from the vaccine coupled with poor compliance with the concomitant antimicrobial therapy (found to be less than 50% after the 2001 US anthrax attacks {Shepard et al, 2002}) could result in increased risk of contracting anthrax.
- potential for comparatively reduced reactogenicity with AV7909 administered using the intramuscular (IM) route. BioThrax is labeled for subcutaneous (SC) administration when used for anthrax PEP, however, it was found in a route and schedule optimization study to be associated with reduced reactogenicity when administered IM vs. SC {Pittman et al, 2002}.

As it is not ethical to perform controlled clinical trials of AV7909 (or any anthrax vaccine) in which humans are purposely exposed to anthrax, nor is it feasible to perform field efficacy trials of AV7909 for the PEP indication given the epidemiology of the disease, Emergent Product Development Gaithersburg Inc. (Emergent) has pursued development of the PEP

indication based upon the US FDA's Animal Rule (Title 21 Code of Federal Regulation [CFR] 601 Subpart H), relying on both animal and human data to demonstrate AV7909 is appropriately safe and immunogenic for this indication.

2.2. Background

Anthrax is an acute infectious disease caused by the spore-forming bacterium *B. anthracis* {CDC, 2017}. It is a zoonotic disease that occurs naturally in many areas of the world, most commonly in agricultural regions with inadequate control programs for anthrax in livestock. The spore form of *B. anthracis* is the predominant phase of the bacterium in the environment and it is largely through the uptake of spores that anthrax is contracted. Resistance to dehydration, heat, ultraviolet light, gamma radiation and many disinfectants makes anthrax spores ideal biological weapons. These spores can be released as an aerosol, dispersed widely and are small enough in size to be inhaled and deposited in the alveoli of the lungs. There are four types of anthrax disease based on how the disease is contracted (cutaneous, gastrointestinal, inhalation, and injection), of which inhalation anthrax occurring after exposure to aerosolized spores is the most lethal form {CDC, 2017}.

While the incidence of naturally acquired anthrax is extremely low in the US, *B. anthracis* has been classified by the Centers for Disease Control and Prevention (CDC) as a Category A Critical Biological Agent, considered to have the potential to cause the greatest harm following deliberate use {NIAID, 2016}. The criteria for placement in this category include severity of impact on human health and high mortality, capacity to cause public panic and social disruption, and special requirements for public health preparedness including the stockpiling of medication.

Virulence components of *B. anthracis* include an antiphagocytic polypeptide capsule and three proteins known as protective antigen (PA), lethal factor (LF), and edema factor (EF). Individually, these proteins are not toxic. However, the combination of PA with LF or EF results in the formation of the cytotoxic lethal toxin and edema toxin, respectively {Liu and Li, 2009}. These toxins inhibit innate immune responses by deregulating pro-inflammatory cytokines, inducing apoptosis in activated macrophages, inhibiting phagocytosis, and suppressing the respiratory burst in polymorphonuclear cells {Phipps et al., 2004}, thus allowing bacteria to replicate unchecked in the host cell.

Numerous studies using animal models of infection have demonstrated that the PA component of the anthrax toxins induces a protective antibody response {Little et al., 2006; Little et al., 2004; Pitt et al., 2001}. Antibodies raised against PA contribute to protection by indirectly neutralizing the activities of the LF and EF toxins {Brachman et al., 2008; Joellenbeck et al., 2002}. In vitro and in vivo studies in various animal models suggest that anti-PA antibodies enhance spore phagocytosis, which inhibits spore germination and leads to increased killing of *B. anthracis* spores by macrophages {Brey , 2005}. AV7909 has been shown to induce anti-PA antibodies in animals and humans {Savransky et al, 2017; Hopkins et al, 2016; Hopkins et al, 2013; Rynkiewicz et al, 2011}.

Animal studies have demonstrated that serum toxin neutralizing antibody (TNA) titer is a reliable predictor of survival following lethal *B. anthracis* challenge {Little et al., 2006;

Little et al., 2004; Pitt et al., 2001}. For PA-based anthrax vaccines, pre-challenge TNA titers correlate with animal survival post-challenge and provide the means for deriving an antibody titer associated with a specific probability of survival in animals {Ionin et al, 2013; Fay et al, 2012}. The TNA assay can selectively quantitate functional antibodies by measuring the ability of serum from immunized animals or human subjects to neutralize lethal toxin {Omland et al, 2008}. Because the assay is species-independent, it can be used to directly compare functional immune response across species, thereby providing a mechanism for bridging animal and human immunogenicity data to support licensure of the vaccine under the FDA's Animal Rule.

In this clinical trial, animal data will be bridged to human data using pre-exposure prophylaxis studies, in which the relationship between the TNA response measured in vaccinated animals immediately prior to *B. anthracis* challenge and animal survival post-challenge will be evaluated and modeled using logistic regression. A TNA 50% neutralization factor (NF_{50}) value associated with a defined probability of survival derived through this logistic function will be used as a threshold of protection in this clinical study to establish vaccine effectiveness. The AV7909-induced TNA antibody titers associated with protection against lethal *B. anthracis* spore challenge at Day 70 were determined in non-human primate (NHP) (Study No. 3655) and guinea pig (GP) (Study No. 3580) pre-exposure efficacy studies (described in Section 2.2.1). As expected, a strong correlation was observed between TNA levels present just prior to challenge and survival rate following challenge. Emergent plans to bridge TNA NF_{50} levels associated with protection defined by 70% survival in animals at the time of challenge (on Day 70 post first-immunization) to Day 64 TNA NF_{50} values in immunized human subjects. Day 64 in the human study represents an approximate time point at which the recommended 60-day antimicrobial regimen would be discontinued in a PEP scenario, a time of heightened risk for humans to be susceptible to any residual anthrax spores. This bridging strategy is similar to that which was used for the BioThrax vaccine for the anthrax PEP indication under the FDA's Animal Rule {Ionin et al, 2013}. Additionally, because AV7909 was shown to induce an accelerated immune response over BioThrax {Rynkiewicz et al, 2011; refer to Section 2.2.2}, protection in animals at the time of challenge on Day 28 post first-immunization will be bridged to Day 29 TNA NF_{50} values in immunized human subjects. Day 29 corresponds to the approximate peak antibody response in humans administered AV7909 IM on Days 1 and 15.

The immune response to AV7909 and safety profile from clinical trials conducted to date are summarized in Section 2.2.2 and Section 2.2.3, respectively. Benefits and risks of AV7909 are described in Section 2.2.3. Refer to the Investigator's Brochure for further details.

2.2.1. Nonclinical Data

Rabbits and NHPs are generally considered the preferred models for inhalation anthrax; however, immunostimulatory activity of CPG 7909 in rabbits has been observed to be significantly weaker compared to the level of activity seen in NHPs, humans, mice, and other vertebrates {Rankin et al, 2001}. Therefore, the immunogenicity and efficacy of anthrax vaccines containing CPG 7909 when evaluated in rabbits may not be predictive of the human

response to such vaccines. Consequently, Emergent developed a GP model of inhalation anthrax and PEP for the purposes of evaluating the efficacy of AV7909.

The Good Laboratory Practice (GLP)-compliant pre-exposure efficacy studies of AV7909 in NHPs and GPs were designed to follow the proposed AV7909 clinical immunization schedule for anthrax PEP. In two separate studies, cynomolgus macaques (Study No. 3655) and Hartley GPs (Study No. 3580) were randomized to one of 16 or 14 groups, respectively. On Days 0 and 14 (corresponds to Days 1 and 15 in the current clinical trial), animals were vaccinated IM per their randomized group assignment with dilutions of AV7909 (1:4 to 1:192 NHPs; 1:64 to 1:512 GPs) or BioThrax (1:64; NHP study only) or with saline (vehicle control). Animals were aerosol-challenged either on Day 28 or Day 70 depending on group assignment with a targeted dose of *B. anthracis* (Ames strain) spores that exceeded the 50% lethal dose by 200 fold (200 LD_{50}). Following challenge, animals were observed for survival for 30 days (NHPs) or 21 days (GPs) post-challenge. Blood collections for TNA (ED_{50} and NF_{50}) were performed prior to vaccination on Day 0 and prior to challenge on Day 28 or Day 70 depending on the group assignment. A logistic regression model was used to estimate pre-challenge TNA NF_{50} titers associated with a 70% probability of survival.

In both studies, immunization induced a rapid, highly protective TNA response. A strong correlation was observed between TNA NF_{50} levels just prior to challenge and survival following challenge. Nonhuman primates challenged on Day 28 and administered AV7909 at either 1:4 or 1:16 dilutions demonstrated the greatest survival rates (100%), as compared with BioThrax-administered (88%) and saline-administered (0%) animals. Additionally, all animals challenged on Day 70 and administered AV7909 at 1:16 dilution survived to study end, in comparison to 25% and 0%, respectively, of BioThrax- and saline-administered animals. Estimates of the Day 28 and Day 70 TNA NF_{50} titers associated with a 70% probability of survival were 0.151 and 0.262 for NHPs challenged on Day 28 or 70, respectively. Notably, the Day 70 TNA threshold of protection derived from NHPs immunized with AV7909 on Days 0 and 14 was similar to that derived from NHPs immunized with BioThrax on Days 0 and 28 (0.29) {BioThrax Prescribing Information, 2015}. Thus, the two week difference in the intervals between the two immunization regimens studied (0, 14 vs 0, 28) did not seem to impact the TNA threshold of protection. The NHP model is considered more biologically relevant than the GP model for comparison to human data.

In the GP study, all animals in the lowest AV7909 dilution group (1:64) challenged on Day 28 and the second lowest dilution group (1:96) challenged on Day 70 survived to study end (100%), in comparison to 0% survival in the saline-administered group. Only one animal each died from groups who received 1:96 or 1:128 dilutions and were challenged on Day 28 or who received 1:64 dilution and were challenged on Day 70, yielding survival rates of 94%. The TNA NF_{50} levels associated with a 70% probability of survival were 0.062 and 0.081 in GPs challenged on Day 28 or on Day 70, respectively.

Single and repeat dose toxicity studies conducted with AV7909 as well as a battery of toxicity tests including reproductive toxicity studies conducted with CPG 7909 revealed no concerns that would preclude testing in humans at the target clinical dose and route of administration. Refer to the Investigator's Brochure for details.

2.2.2. Clinical Immunogenicity

Three clinical studies have been completed as part of the AV7909 development program in which 342 healthy adults were enrolled, 241 of them exposed to the combination of AVA plus CPG-7909. Throughout this text, AVA is used to refer to BioThrax.

Study V011

The first-in-man, proof-of-concept study (Study V011) was conducted by Coley Pharmaceutical Group, Inc. (now part of Pfizer Inc.) to determine the safety and characterize the immunogenicity of AVA admixed (at bedside) with CPG 7909 prior to injection in healthy subjects aged 18 to 45 years, inclusive {Rynkiewicz et al, 2011}. Sixty-nine subjects were randomized to receive a standard dose (0.5 mL) of AVA alone, 1.0 mg of CPG 7909 alone, or the standard dose of AVA admixed prior to injection with 1.0 mg of CPG 7909. All subjects received vaccinations IM on Days 0, 14, and 28. Immunogenicity and safety were evaluated until 28 days following the final injection. Immunogenicity endpoints included the serum concentrations of TNA.

The geometric mean peak TNA concentration for the AVA plus CPG 7909 arm was 1570 µg/mL, which was 8.8-fold higher than that observed for the AVA-alone group of 178 µg/mL ($p<0.001$, t-test). In this study, AVA_{max} was defined as the geometric mean of the highest (peak) TNA concentrations for subjects in the AVA-alone arm at Day 42, 49, or 56 (2 to 4 weeks after the third injection). AVA_{max} by TNA was determined to be 159 µg/mL. The median time to reach this concentration for the AVA plus CPG 7909 arm was 21 days, a 25-day acceleration over the median 46 days it took for the AVA alone arm to reach this concentration.

Study EBS.AVA.201

The next clinical study, EBS.AVA.201, was conducted by Emergent as a phase 1b, parallel-arm, double-blind, randomized, placebo-controlled, dose-ranging study evaluating the safety, tolerability and immunogenicity of AV7909 in healthy adults aged between 18 and 50 years, inclusive {Hopkins et al, 2013}. The purpose of the study was to determine if a decrease in the amount of AVA or CPG 7909 per dose (compared to 0.5 mL of AVA and 1.0 mg of CPG 7909 used in Study V011) could decrease the reactogenicity of this vaccine, while still maintaining increased and accelerated peak immunogenicity. EBS.AVA.201 was designed to measure the TNA response after two doses of vaccine, given 2 weeks apart through the end of an 84-day study period. Four pre-formulated combinations of AVA plus CPG 7909 (AV7909) were compared with AVA alone and saline placebo in a 6-arm study enrolling 105 subjects. AV7909 was formulated so that a 0.5 mL dose contained either 0.5 mL or 0.25 mL of AVA and either 0.5 mg or 0.25 mg of CPG 7909: Formulation 1 = 0.5 mL AVA + 0.5 mg CPG 7909; Formulation 2 = 0.5 mL AVA + 0.25 mg CPG 7909; Formulation 3 = 0.25 mL AVA + 0.5 mg CPG 7909; and Formulation 4 = 0.25 mL AVA + 0.25 mg CPG 7909. Subjects received vaccinations via the IM route on Days 0 and 14. Immunogenicity was evaluated via serum TNA assays through Day 84 and safety was evaluated up through follow-up phone contacts on Days 194 and 374.

In the AV7909 arms, geometric mean TNA (NF_{50}) values began increasing after Day 14 with peak levels achieved at Day 28 and gradually declining thereafter to Day 84. Mean values

were still above baseline at Day 84 in all active treatment groups. The highest geometric mean TNA (NF_{50}) value on Day 28 was achieved with Formulation 2 (3.85), followed by Formulation 1 (3.05), Formulation 3 (2.54), and Formulation 4 (1.73). Day 28 geometric mean TNA NF_{50} values were 0.13 in the AVA group and 0.03 (below the limit of quantification) in the saline placebo group. There were no statistically significant differences between the AV7909 groups in geometric mean TNA values at any of the visits between Days 21 and 84.

A post-hoc analysis was performed to determine the proportion of subjects who met or exceeded the TNA NF_{50} threshold of protection of 0.56, which is associated with 70% survival in rabbits administered AVA IM on a Days 0 and 28 schedule and challenged on Day 70 with a 200 LD_{50} targeted dose of aerosolized *B. anthracis* spores. This target value had previously been accepted by CBER as an appropriate threshold of protective immunity for BioThrax (AVA without CPG 7909). For Formulations 1, 2, and 3, the highest TNA NF_{50} levels were achieved on Days 28, 35, and 42. The percentages of subjects reaching a TNA NF_{50} value of 0.56 at these visits were 94% to 100%, 94%, and 88% to 89% for Formulations 1, 2, and 3, respectively. The percentages declined after Day 42; however, Formulation 2 still demonstrated a large proportion of subjects over the threshold of protection at Day 70 (81%) compared with Formulation 1 (77%) and Formulation 3 (61%). The percentage of subjects achieving a TNA NF_{50} value at or above 0.56 with Formulation 4 was lower than with the other AV7909 formulations at each study visit.

As Formulation 2 containing 0.5 mL AVA and 0.25 mg CPG 7909 was associated with the highest immune response at Day 28 and found to be more tolerable for reactogenicity, it was selected for further development (see Section 4.3).

Study EBS.AVA.208

Emergent's phase 2 study, EBS.AVA.208, was designed as a randomized, double-blind, active-controlled, parallel-group study to evaluate the safety and immunogenicity of three immunization schedules and two dose levels of AV7909 in healthy adults aged 18 to 50 years, inclusive {Hopkins et al, 2016}. The primary objectives were to assess safety and to assess immunogenicity as measured by TNA NF_{50} values for each study arm at Day 63. Schedule and dose optimization were evaluated. A total of 168 subjects were randomized to one of five arms, as follows:

- Arm 1, two doses of AV7909 given 2 weeks apart on Days 0 and 14
- Arm 2, two doses of AV7909 given 4 weeks apart on Days 0 and 28
- Arm 3, three doses of AV7909 given 2 weeks apart on Days 0, 14, and 28
- Arm 4, three half doses of AV7909 given 2 weeks apart on Days 0, 14, and 28
- Arm 5, three doses of AVA given 2 weeks apart on Days 0, 14, and 28

In all arms, vaccine was administered via the IM route in the deltoid muscle. Placebo (saline for injection) was used in Arms 1 and 2 to maintain the study blind. Safety was evaluated through telephone follow-up calls 6 months and 12 months after the last scheduled vaccination.

The primary outcome measure in this study – lower bound (LB) of the two-sided 95% confidence interval (CI) for the proportion of subjects in each arm with TNA NF_{50} ≥0.56 at Day 63 – was based on the correlate of protection derived from a pre-exposure animal model challenge study using AVA in rabbits {BioThrax Prescribing Information, 2015}. Nonclinical studies to determine a TNA NF_{50} threshold specific for AV7909 using appropriate animal models were ongoing at the time of study initiation. Hence, the correlate derived from an AVA study was used. For the primary immunogenicity outcome measure, the criterion for success was that the LB of the two-sided 95% CI for the proportion of subjects who reached the TNA threshold (TNA NF_{50} ≥0.56) is ≥40% on Day 63.

For the first two secondary immunogenicity outcome measures, the same immunogenicity analysis as for the primary outcome measure was performed at earlier time points (eg, Day 28 and Day 42), using the same success criterion (≥ 40%).

At Day 63, the 95% CI LB values for the proportions of subjects meeting or exceeding the 0.56 TNA NF_{50} threshold in descending order were 87.2% for Arm 2, 81.5% for Arm 3, 76.9% for Arm 4, 39.5% for Arm 1, and 29.8% for Arm 5. Therefore, the primary outcome measure of achieving the success criterion (LB being ≥40%) was successfully met by Arms 2, 3, and 4, but not by Arm 1 (which just missed the success criterion at 39.5%) or Arm 5. While the result for Arm 5 (AVA) differs from previous AVA studies {Ionin et al, 2013}, this observation may be partially explained by use of the IM route of administration (versus the SC route) and/or the small sample size which contributed to a larger confidence interval.

The secondary outcome measure of achieving a 95% CI LB of ≥40% for the proportion of subjects with TNA NF_{50} ≥0.56 at Day 28 was successfully met by Arms 1, 3, and 4 and at Day 42 was successfully met by all study arms.

Despite Arm 1 not achieving the success criterion for the primary endpoint at Day 63, the two-dose Days 0 and 14 AV7909 schedule utilized in Arm 1 was selected for phase 3 evaluation, as it showed a comparable immune response to the Days 0, 14 and 28 AVA vaccine schedule with the added advantage of a higher and earlier TNA NF_{50} peak.

In the current phase 3 trial, Emergent chose to assign study Day 1 to the day that participants will receive their first vaccination. Consequently, the two dose schedule for AV7909 (or three dose schedule for BioThrax) on Days 1 and 15 (and 29) in this trial corresponds to the Days 0 and 14 (and 28) schedule in the previous trials where Day 0 was assigned as the day of first vaccination.

2.2.3. Clinical Safety

During clinical testing in which 241 subjects were exposed to the combination of AVA + CPG 7909, systemic reactogenicity manifested primarily as mild to moderate fatigue, muscle ache and headache. The most common local reactions were mild to moderate pain, tenderness and arm motion limitation. These reactions often resolved within 48 hours after dosing without treatment or with non-steroidal anti-inflammatory drugs to treat the more severe or prolonged symptoms.

The most common adverse events (AEs) with AV7909 (reported in ≥20% of subjects in the AV7909 arm(s) across the three completed clinical trials) were various forms of injection site

reaction (including injection site pain, movement impairment, warmth, edema, erythema, induration, haemorrhage, and pruritus), fatigue, myalgia, headache, respiratory rate increased, hypokalaemia, pyrexia, lymphocyte count decreased, pharyngolaryngeal pain, nausea, leukopenia, upper respiratory tract infection, hypoglycaemia, chills, blood creatine phosphokinase increased, white blood cell count decreased, and haemoglobin decreased.

A single death was reported across the three trials, resulting from automobile accident in a male subject in the Formulation 1 arm (AVA 0.5 mL + CPG 7909 0.5 mg) of Study EBS.AVA.201. The death was recorded at the time of the 12-month safety follow-up phone contact and considered by the investigator to be unrelated to the study product.

Serious adverse events (SAEs) have been reported for seven subjects in the AV7909 program, none of which were determined as being related to the study product by the investigators. Four of the seven subjects having SAEs received AV7909. These included two subjects in Study EBS.AVA.201 (the subject in the Formulation 1 arm who died of an automobile accident; and a male subject in the Formulation 2 arm [AVA 0.5 mL + CPG 7909 0.25 mg] for whom stage 4 glioblastoma multiforme was diagnosed on Day 113) and two subjects in Study EBS.AVA.208 (male subject in Arm 1 [AV7909 administered on Days 1, 14] who withdrew from the study on Day 48 because of cellulitis secondary to an animal bite and later, at the time of the 12-month phone contact after the last vaccination, reported a cancer down near the rectum that could not be independently verified by study personnel; and atelectasis neonatal reported for the female infant of a woman in Arm 1 who became pregnant after Day 84). The atelectasis neonatal in the female patient's female infant was considered attributable to the precautionary early caesarean section performed at 36 weeks because of the mother's bicornuate uterus. Two of the seven subjects having SAEs received AVA: a male subject in Study V011 experienced tonic clonic seizure 25 days after the third injection of AVA; and a female subject in Study EBS.AVA.208 (Arm 5) had a severe AE of pyelonephritis that started 35 days after the first dose.

Treatment with AV7909 and AVA has been generally well tolerated, with a low rate of vaccination discontinuations because of AEs, ranging from 2.2% (1/46, Study V011; 2/90, Study EBS.AVA.201) to 4.2% (7/168; Study EBS.AVA.208) for a total of ten subjects. In Study V011, vaccination was suspended in one subject for an AE of Grade 2 (moderate) disseminated rash that occurred after his second injection of AVA + CPG 7909. This was considered by the investigator to be probably related to the study product, suggestive of an allergic reaction. In Study EBS.AVA.201, two subjects had AEs leading to discontinuation of the study product:

- One subject in the AVA arm had a mild upper respiratory tract infection on Days 13 to 31 that was assessed by the investigator as unrelated to the study product. This was associated with a Grade 2 (moderate) elevated temperature (101.8 ºF) on Day 14 that precluded the second vaccination.
- One subject in the Formulation 1 arm (AVA 0.5 mL + CPG 7909 0.5 mg) had an AE of decreased lymphocyte count on Day 1 after the first injection. The event was considered by the investigator to be severe and definitely related to the study

product. The event resolved without sequelae on Day 2. Vaccination was discontinued due to this event.

In Study EBS.AVA.208, nine AEs led to discontinuation of the study product in seven subjects, all of whom had received AV7909. A proportionally higher number of subjects discontinued the study product due to an AE in Arm 1 (5/44; 11.4%) compared to the other study arms (2.9% [1/34] in Arm 2 and 4.3% [1/23] in Arm 3; none in Arms 4 or 5). Six of the nine AEs that led to discontinuation of study product were assessed and determined by the investigator to be related to the study product: alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased (in the same subject/Arm 1; both events moderate); pruritus generalised and rash (in the same subject/Arm 2; both events mild); injection site erythema (1 subject/Arm 3; severe); and a second event of rash (1 subject/Arm 1; moderate). The AEs leading to discontinuation of study product of cellulitis (severe), nasopharyngitis (mild), and urticaria (moderate) were assessed and determined by the investigator to be unrelated to the study product (all in Arm 1).

No AESIs of potential autoimmune etiology were reported in any of the AV7909 studies.

With respect to clinical laboratory abnormalities, in Study V011, hypokalemia was reported in 50% (11/22), 43.5% (10/23), and 62.5% (15/24) of participants in the AVA, CPG 7909, and AVA + CPG 7909 groups, respectively, in subjects who met Grade 1 (≥3.3 to <3.5 mEq/L) to Grade 3 (≥3.0 to <3.2 mEq/L) and 1 subject in the CPG 7909 group who met Grade 4 (<3.0 mEq/L) toxicity criteria, suggesting that potassium levels may have been affected by the various treatments. In Study EBS.AVA.201, hematology results showed a trend towards decreased absolute lymphocyte count (ALC) on Day 1 after the first vaccination and a trend towards decreased absolute neutrophil count (ANC) and white blood cell count (WBC) on Day 2 after the first vaccination in all AV7909 groups. Differences in ALC or ANC between study groups were not notable by Day 7. AV7909 formulations with 0.5 mg of CPG 7909 (Formulations 1 and 3) were associated with greater decreases in the ANC on Days 2 and 7. In Study EBS.AVA.208, Grade 3 or higher laboratory abnormalities were reported in subjects for the laboratory parameters of hemoglobin, AST, glucose (blood), glucose (urine), protein (urine) and erythrocytes (urine). There were no clinically relevant differences in incidences between study arms, except that the proportion of subjects with erythrocytes in urine was higher in Arm 5 (5/23, 21.7%) compared to Arms 1-4 (0% to 5/44 or 11.4%).

2.3. Benefit/Risk Assessment

2.3.1. Benefits

No benefits can be guaranteed to individuals participating in this study. Participants will be contributing to research that may result in the licensure of the next generation anthrax vaccine for PEP having a more convenient dosing schedule and generating an earlier immune response than the currently licensed BioThrax vaccine.

2.3.2. Risks

The risks associated with AV7909 are similar to those described for BioThrax and CPG 7909 since AV7909 is a combination of the two products.

Since the licensure of BioThrax in 1970, more than 3.3 million individuals, primarily military personnel, have been vaccinated in the pre-exposure setting {BioThrax.com, 2016}. The safety profile of BioThrax and its associated risks are summarized in the BioThrax prescribing information {BioThrax Prescribing Information, 2015}.

CPG 7909 has been investigated clinically since the mid-1990s for indications that have included cancer monotherapy, combination use with anti-cancer therapies, and vaccine adjuvant against infectious diseases and cancers. A literature search conducted by Emergent yielded 21 completed infectious disease studies using CPG 7909 as a vaccine adjuvant in primarily healthy subjects, including the trials of the AV7909 program. These studies covered the dose range and route of administration (IM) used in the AV7909 clinical studies and are most relevant for the risk evaluation (refer to the Investigator's Brochure for details).

Hypersensitivity and Anaphylactic/Anaphylactoid Reactions

Acute allergic reactions, including anaphylaxis, have occurred with BioThrax {BioThrax Prescribing Information, 2015}. Parenteral administration of any protein product may be associated with immediate-type hypersensitivity reactions that can manifest as urticaria, shortness of breath, wheezing, nausea and cramping, and in severe cases, hypotension. In the AV7909 program, a report of urticaria after the second vaccination with AV7909 (AV7909 Arm 1; Study EBS.AVA.208) resolved with diphenhydramine hydrochloride. The subject 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 for a subject in the AV7909 Formulation 1 arm, which was treated and resolved after two days and considered possibly related to study product administration. Two subjects 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. In Study V011, two subjects in the AVA + CPG 7909 arm had hypersensitivity reactions considered by the investigator to be unlikely related to study product administration; and a subject 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. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

BioThrax and AV7909 vaccine are not to be administered to subjects with known sensitivity to any of the vaccine components, eg, synthetic ODNs, formaldehyde, benzethonium chloride (phemerol), or aluminum.

Additionally, as the stopper of the vials for BioThrax vaccine contains natural rubber latex and may cause allergic reactions in latex-sensitive individuals, BioThrax is not to be administered to subjects with latex allergy.

Adverse Events of Autoimmune Etiology

There is a potential for CpG ODN adjuvants to trigger autoimmune disease in susceptible individuals {Segal et al 2000}, possibly as a result of non-specific activation of T or B lymphocytes. No subjects in the completed AV7909 clinical trials have reported AEs related to autoimmune disorders. Additionally, no AEs suggestive of autoimmune disease have been reported in the reviewed published data on the CPG 7909-adjuvanted infectious disease vaccine trials. A number of these trials reported subjects with moderate, transient elevations above the normal range in anti-double stranded deoxyribonucleic acid (anti-dsDNA) values or positive antinuclear antibody (ANA) or mild elevations in rheumatoid factor (RF) following vaccination, which typically returned to normal by the next dose or end of the study and were not associated with clinical symptoms {Ellis et al, 2010; Mullen et al, 2008; Cooper et al, 2005; Cooper et al, 2004}. In a phase 3 trial of Heplisav-B vaccine containing a different CpG ODN, CpG 1018, in subjects followed for 13 months after the first dose of vaccine, the incidences of new onset immune-mediated AEs (as reviewed by independent adjudicators) were not clinically different between the Heplisav-B group (0.1%; 4/5587) and the non-adjuvanted Energix-B group (0%; n=2781), nor were these AEs in the Heplisav-B group considered related to vaccination {Heplisav-B Prescribing Information, 2017}.

In oncology trials of CPG 7909 that typically have used higher doses and treatment durations than expected with AV7909 vaccine exposure (refer to the Investigator's Brochure for more details), autoimmune disease has been reported in multiple subjects, although causal attribution to the study product is complicated by comorbidities and concomitant products/therapies. The autoimmune conditions observed have included polyarthralgia, arthritis, Sjögren's Syndrome, autoimmune thyroiditis, vitiligo, Guillain-Barré syndrome, and ulcerative colitis.

Because of this potential risk, the enrollment of individuals with a history of autoimmune disorders or active autoimmune disease will be prohibited in the current trial. Additionally, because of the possibility for a delay between the vaccination and onset of symptoms indicative of a disease process, all participants will be followed for potential adverse events of autoimmune etiology up to Month 13 (nominally for 12 months after the last vaccination). Such AEs will be captured as "adverse events of special interest [AESI]" referring to the list of autoimmune disorders compiled by CBER and listed in Appendix B. Blood samples will be collected at specified time points from all participants for auto-antibody testing. Participants who discontinue study treatment will be encouraged to attend all subsequent clinic visits and safety follow-up contacts to facilitate this monitoring.

Pregnancy and Lactation

No reproductive toxicity studies have been performed with AV7909. BioThrax can cause fetal harm when administered to a pregnant woman {BioThrax Prescribing Information, 2015}. CPG 7909 had been determined to be embryolethal in rabbits and teratogenic in developing rats and rabbits at doses far in excess of the individual vaccination dose for anthrax PEP (0.25 mg). In rats, fetal skeletal anomalies were noted (>3 mg/kg/day); in rabbits, slightly reduced numbers of viable fetuses (3 mg/kg/day), and external, visceral, and skeletal malformations occurred (>1 mg/kg/day).

Consequently, breastfeeding and a positive pregnancy test will preclude study enrollment. All women of childbearing potential must additionally have a negative pregnancy test before each vaccine administration, and must use effective contraception from at least one month prior to Day 1 and continued through Month 13. Confirmed pregnancy will result in discontinuation of vaccinations. Participants must be monitored for pregnancy outcomes according to protocol-specified procedures.

Injections

Potential risks associated with both IM and SC injections include nerve or blood vessel damage, dizziness, fainting, infection, sterile abscess, and pain associated with a needle stick. Potential risks associated with venipuncture include pain/tenderness, swelling, bleeding, bruising, dizziness, and infection.

Refer to the Investigator's Brochure for further details.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Study objectives are as follows:

Primary:

- To demonstrate lot consistency following a two-dose schedule of AV7909 (Days 1 and 15) administered IM in healthy adults.
- To demonstrate immunogenicity under the US FDA's Animal Rule on Day 64 following a two-dose schedule of AV7909 (Days 1 and 15) administered IM in healthy adults.
- To demonstrate immunogenicity using the US FDA's Animal Rule at Day 64 based on the noninferiority of a two-dose schedule of AV7909 (Days 1 and 15) administered IM to the licensed three-dose schedule of BioThrax (Days 1, 15, and 29) administered SC in healthy adults.
- To evaluate the safety of AV7909 in healthy adults following a two-dose schedule (Days 1 and 15) administered IM.

Secondary:

- To demonstrate immunogenicity under the US FDA's Animal Rule on Day 29 following a two-dose schedule of AV7909 (Days 1 and 15) administered IM in healthy adults.

3.2. Study Endpoints

3.2.1. Primary Endpoints

The primary study endpoints are as follows:

Lot Consistency:

- Equivalent immunogenicity across three consecutive AV7909 lots as demonstrated by the 95% CI for the ratios of geometric mean TNA NF_{50} at Day 64 for each of the three lot-to-lot comparisons to be within 0.5 and 2.0.
- Protective level of immunogenicity in all three consecutive AV7909 lots as demonstrated by the LB of the two-sided 95% CI to be ≥40% for the proportions of AV7909 subjects in each of the three lots achieving a TNA NF_{50} ≥0.56 at Day 64.

Immunogenicity:

- Lower bound of the two-sided 95% CI is ≥40% for the proportion of AV7909 participants in Groups 1-3 (three lots pooled) achieving a TNA NF_{50} ≥0.56 on Day 64.

- Non-inferiority of AV7909 to BioThrax at Day 64 as determined by the two-sided lower 95% CI of the difference in the proportion of AV7909 participants (three lots pooled) with a TNA $NF_{50} \geq 0.29$ and the proportion of BioThrax participants with a TNA $NF_{50} \geq 0.29$ being greater than -15%.

Safety:

- Incidences of SAEs from the time of the first vaccination on Day 1 through the 12-month safety follow-up telephone call following the last vaccination.

3.2.2. Secondary Endpoints

The secondary study endpoints are as follows:

Immunogenicity:

- Lower bound of the two-sided 95% CI will be ≥67% for the proportion of AV7909 participants in Groups 1-3 (three lots pooled) achieving a TNA $NF_{50} \geq 0.15$ on Day 29.

Safety:

- Incidences of AEs from the time of the first vaccination on Day 1 through Day 64
- Incidences of clinical laboratory abnormalities
- Incidences of autoimmune-associated AESIs from the time of the first vaccination on Day 1 through the 12-month safety follow-up telephone call following the last vaccination
- Incidences of solicited systemic reactions and solicited injection site reactions by severity following each vaccination as reported in participant e-diaries

4. STUDY DESIGN

4.1. Overall Study Design

This is a phase 3, multicenter, randomized, double-blind, parallel-group trial designed to evaluate the lot consistency (using three consecutive lots), immunogenicity, and safety of a two-dose schedule of AV7909 (Days 1 and 15) administered IM in healthy adults for an indication of PEP of anthrax.

Healthy adults between 18 and 65 years of age (inclusive) will sign and date an informed consent form and then be screened for eligibility for participation in the study 2 to 28 days prior to randomization. Participants meeting the entry criteria will be randomized 2:2:2:1 (block size of 7) to one of four study groups on Day 1, as shown in Table 2. Randomization will be stratified by site. Racial distribution will be monitored among recruited participants. Participants who are randomized and do not receive vaccination on the same day will be withdrawn from the study.

Table 2: Study Groups

Group No./Treatment	Sample Size (N)	Day 1	Day 15	Day 29
1/AV7909 Lot 1	1100	AV7909 Lot 1 (IM)	AV7909 Lot 1 (IM)	Placebo (SC)
2/AV7909 Lot 2	1100	AV7909 Lot 2 (IM)	AV7909 Lot 2 (IM)	Placebo (SC)
3/AV7909 Lot 3	1100	AV7909 Lot 3 (IM)	AV7909 Lot 3 (IM)	Placebo (SC)
4/BioThrax	550	BioThrax (SC)	BioThrax (SC)	BioThrax (SC)
Total	3850			

IM = intramuscular injection in the deltoid muscle; SC = subcutaneous injection over the deltoid region.

The study schematic is provided in Figure 1.

Blood samples for immunogenicity testing will be collected prior to vaccination on Day 1 (baseline) and on Days 29 and 64 and assayed using toxin neutralization assay. The assay results will be reported as the reciprocal of a serum sample dilution that results in 50% neutralization of cytotoxicity of the lethal toxin (50% effective dilution; ED_{50}). To standardize assay results, the results will be divided by the ED_{50} of a serum reference standard, and the resulting ratio will be reported as a 50% neutralization factor (NF_{50}).

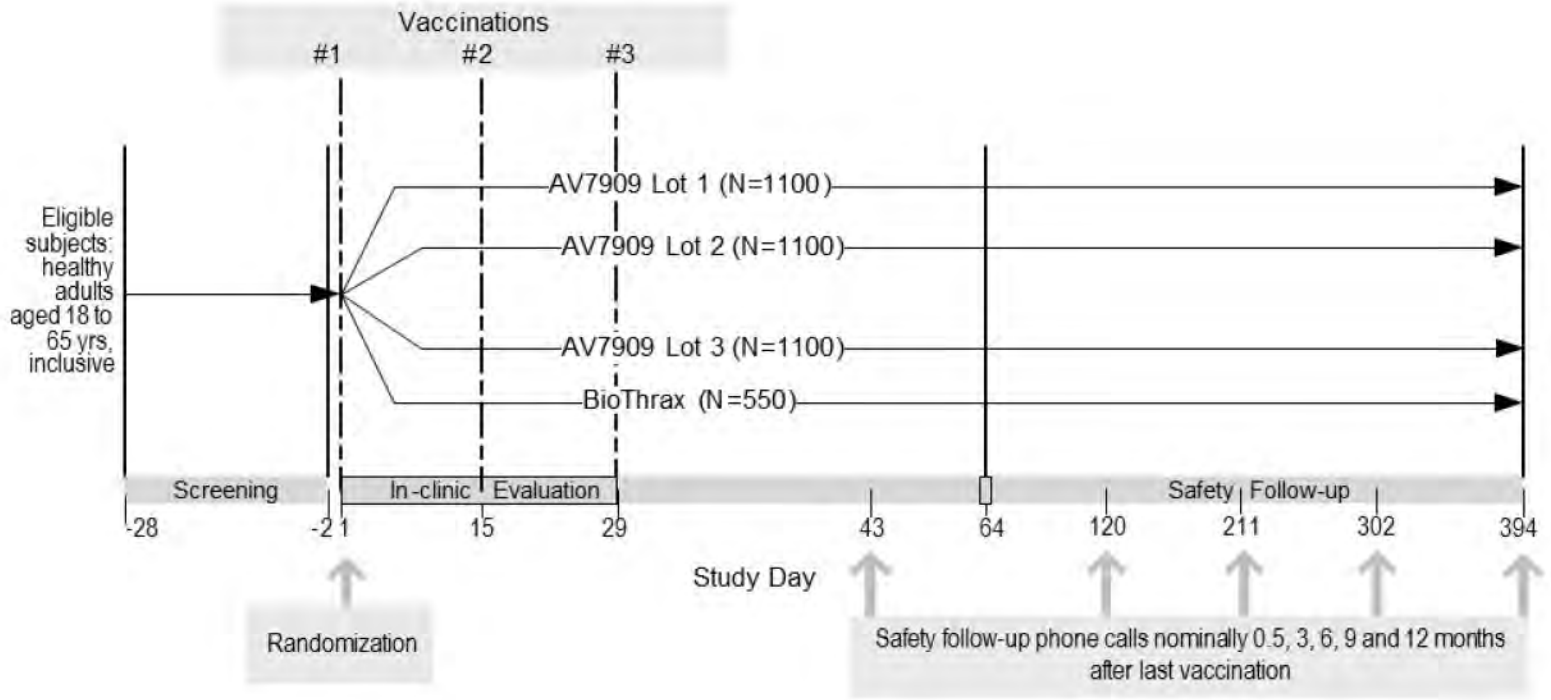
Participants will be evaluated for safety through Day 64 (or the early withdrawal visit [EWV]), as assessed by clinical laboratory tests (hematology, serum chemistry, and urinalysis), monitoring of AEs including SAEs and AESIs, vital signs, and physical examinations (PEs). Adverse events of special interest are AEs associated with autoimmune disease as defined by the Center for Biologics Evaluation and Research [CBER]; refer to Appendix B), and might 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 Preventative Vaccine Clinical Trials* (refer to Appendix A). Reactogenicity (solicited systemic and injection site reactions) will be assessed daily by the participants using e-diaries for at least seven days after each vaccination. If

injection site or systemic reactions continue beyond seven days, participants will be prompted to continue e-diary entries until resolved for at least two consecutive days. Use of medications will be collected at each study visit. In addition, blood samples for auto-antibody assessment will be taken at Day 1 predose and Day 64 (or EWV) for testing for rheumatoid factor (RF), antinuclear antibody (ANA) and anti-double stranded deoxyribonucleic acid (dsDNA) antibodies, and thyroid-stimulating hormone (TSH). To ensure a robust safety follow up, participants who receive at least one dose of vaccine but for any reason discontinue vaccinations prematurely will be asked to participate in the further planned study visits up to Day 64 for safety assessment only.

Participants who receive at least one dose of vaccine will also participate in safety follow-up phone calls occurring on Day 43, Month 4 (Day 120), Month 7 (Day 211), Month 10 (Day 302), and Month 13 (Day 394); ie, nominally 0.5, 3, 6, 9, and 12 months after the last vaccination to collect information on AEs, SAEs and any potential AESIs. Based on responses at these phone contacts, participants may be asked to return to the clinic for an unscheduled visit to provide blood samples for auto-antibody testing 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 (refer to Section 8.4.1) as determined by the 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. A planned interim DSMB safety data review will be conducted after the first 500 participants have completed the Day 29 visit, comprising all safety evaluations through two weeks after the second vaccination. All DSMB reviews will be performed with blinded data, unless otherwise requested by the DSMB Chair. 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.

Figure 1: Study Design Schematic



IM = intramuscular; SC = subcutaneous.
AV7909 is administered IM on Days 1 and 15, with placebo administered SC on Day 29.
BioThrax is administered SC on Days 1, 15, and 29.

4.2. Scientific Rationale for Study Design

This licensure-enabling study is designed in accordance with FDA's Animal Rule. As a result, the study relies on derived immune correlates of protection from animal studies (TNA NF_{50} values), which are used to bridge observed immunogenicity responses and survival rates in vaccinated animals post-anthrax challenge to observed immunogenicity responses and predicted survival probability in humans. AV7909 immunogenicity is intended to be demonstrated by:

- the generation of an antibody response at Day 64 in humans administered AV7909 that has been determined as protective in animals (primary endpoint). Day 64 is the anticipated time point at which concomitant antimicrobial therapy would be completed, which is a time of heightened risk for humans to be susceptible to any residual anthrax spores.
- the noninferiority at Day 64 of the antibody response (at levels determined as protective in animals) in humans administered AV7909 to the antibody response (at levels determined as protective in animals) in humans administered BioThrax (primary endpoint). BioThrax was selected as the active control in this study as it is the only vaccine currently licensed in the US for anthrax PEP. Moreover, BioThrax (AVA) is a component of AV7909 vaccine.
- the generation of an antibody response at Day 29 in humans administered AV7909 that has been determined as protective in animals (secondary endpoint). Day 29 is the time point of approximate peak antibody response with a Days 1 and 15 vaccination schedule for AV7909, occurring two weeks after the second/last vaccination.

To demonstrate a protective antibody response in humans at Day 64 with a two-dose schedule of AV7909, the proportion of AV7909 participants in Groups 1-3 (three lots pooled) achieving a TNA $NF_{50} \geq 0.56$ on Day 64 will be determined. This threshold of protection (0.56) is based on the Day 70 TNA NF_{50} value associated with 70% survival in rabbits administered BioThrax IM on Days 0 and 28 and challenged on Day 70 with *B. anthracis* spores (Study 646) {BioThrax Prescribing Information, 2015} {Ionin et al, 2013}. Use of this threshold is appropriate as it was part of the basis for BioThrax licensure for anthrax PEP and represents the most conservative (highest) threshold value from three species (rabbits, GPs, and NHPs) evaluated with BioThrax or AV7909. For this endpoint, the success criterion to establish Day 64 protective immunity in humans − lower bound (LB) of the two-sided 95% CI for the proportion of participants achieving the threshold being greater than or equal to 40% − has its basis in the BioThrax PEP clinical development program, where 40% was utilized as a conservative measure corresponding to adequate vaccine efficacy {BioThrax Prescribing Information, 2015}.

To determine if a two-dose, two-weeks apart schedule of AV7909 is noninferior to a three-dose, two-weeks apart schedule of BioThrax for PEP of anthrax at Day 64 (time of approximate completion of the concomitant antimicrobial therapy), the proportions of AV7909 participants (Groups 1-3 pooled) and of BioThrax participants achieving a TNA NF_{50} value ≥ 0.29 will be determined. The 0.29 threshold of protection is based on the Day 70 TNA NF_{50} value associated with 70% survival in NHPs administered BioThrax IM on Days 0 and 28 and challenged on Day 70 with *B. anthracis* spores (Study 844) {BioThrax Prescribing Information, 2015} {Ionin et al,

2013}. Use of the 0.29 threshold is appropriate for this non-inferiority analysis as 1) NHP is the only animal species for which the immune correlate of protection has been established for both BioThrax and AV7909; and 2) this value represents a more conservative (higher) threshold that is moreover substantially similar to the threshold derived from the corresponding AV7909 NHP pre-exposure efficacy study (0.26; refer to Section 2.2.1). Noninferiority will be declared if the lower 95% confidence limit of the difference in the proportion of participants (AV7909 minus BioThrax) is greater than -15%.

To demonstrate a protective antibody response in humans at Day 29 with a two-dose schedule of AV7909, the proportion of AV7909 participants in Groups 1-3 pooled achieving a TNA NF_{50} value $\geq$0.15 on Day 29 will be determined. The threshold of protection (0.15) is based on the Day 28 TNA NF_{50} value associated with 70% survival in NHPs administered AV7909 on Days 0 and 14 and challenged with *B. anthracis* spores on Day 28 (Study 3655; unpublished data; refer to Section 2.2.1). For this endpoint, the success criterion to establish Day 29 protective immunity in humans is the LB of the two-sided 95% CI for the proportion of participants achieving threshold being greater than or equal to 67%. This more stringent criterion was selected since protection on Day 29 may support use of a shorter course of concomitant prophylactic antimicrobials.

Because lot-to-lot variability in the manufacture of AV7909 is expected, this study is additionally designed to demonstrate consecutively-manufactured lots of AV7909 confer a consistent antibody response in humans based on equivalence in the TNA NF_{50} response at Day 64 across three lots tested (Groups 1 to 3). Equivalence bounds of 0.5 to 2.0 will be used for the 95% CI for the geometric mean (GM) ratio for all three pairwise lot-to-lot comparisons. These equivalence bounds are set higher than the usual convention based on the lot-to-lot variability observed with BioThrax (where the lot-to-lot geometric mean titer [GMT] ratio in TNA NF_{50} could be as low as 0.6) and, lacking clinical data with AV7909, the supposition that more variability is likely to be observed with AV7909, given the addition of CPG 7909 and the more diverse subject demographics planned for the phase 3 trial. Because of this, a co-primary lot consistency endpoint was added, to demonstrate a protective immune response individually in all three lots tested based on the proportions of subjects achieving a TNA NF_{50} $\geq$0.56 at Day 64.

4.3. Justification for Dose and Schedule

Dosing in the active control group (Group 4; BioThrax) is consistent with the BioThrax prescribing information for anthrax PEP, which requires vaccinations administered SC at 0, 2, and 4 weeks postexposure combined with antimicrobial therapy {BioThrax Prescribing Information, 2015}. Since participants in this study will not have actually been exposed to anthrax spores, concomitant antimicrobial therapy will not be provided to any participant.

The IM route of administration was selected for the AV7909 program starting with the first AV7909 trial, Study V011, because of anticipated less reactogenicity as compared with SC administration that was reported in a Department of Defense schedule and route optimization study for BioThrax {Pittman et al, 2002}. Dose selection for Study V011 was based on the licensed schedule of primary series of injections used at the time for AVA (0.5 mL administered at 0, 2, and 4 weeks) and the highest CPG 7909 dose tested (1 mg) in a phase 1/2 study in which CPG 7909 was evaluated with a licensed hepatitis B vaccine (Engerix-B®, GlaxoSmithKline)

and found to be both immunogenic and safe/tolerated {Cooper et al, 2004}. An observation in Study V011 of increased frequency and severity (more Grade 2 reactions) of injection site reactions along with systemic AEs including fatigue, headache, myalgia, and nausea in the BioThrax + CPG 7909 group compared to the BioThrax alone or CPG 7909 alone groups {Rynkiewicz et al, 2011} led to a subsequent phase 1b formulation optimization study. In this study (EBS.AVA.201), subjects received four different formulations of AV7909 as two doses given two weeks apart using combinations of 0.25 or 0.5 mL AVA and 0.25 mg or 0.5 mg CPG 7909 {Hopkins et al, 2013}. AV7909 Formulation 2, containing 0.5 mL AVA and 0.25 mg CPG 7909, was selected for further development based on the following observations/suppositions:

- Decreasing the AVA content from 0.5 mL to 0.25 mL trended towards inferior immunogenicity
- Increasing the CPG 7909 content from 0.25 mg to 0.5 mg increased the incidence and severity of both local and systemic reactions as assessed with a subject diary without enhancing immunogenicity
- Injection site reactogenicity appeared similar to that for BioThrax
- A lower amount of unbound CPG in Formulation 2 could potentially reduce the risk of off-target immune activation
- The proportion of subjects with a TNA $NF_{50} \geq 0.56$ (eg, threshold of protection for BioThrax) was over 85% at Day 56 for this formulation, a time when around 50% of subjects would typically discontinue antibiotics

The AV7909 vaccine schedule planned for use in the current phase 3 study was confirmed by the results of the phase 2 schedule and dose optimization study (EBS.AVA.208) that used Formulation 2 from Study EBS.AVA.201 {Hopkins et al, 2016}. In this study, a rapid and durable immune response was observed with two IM doses of AV7909 given two weeks apart. While the results using this route/schedule marginally missed the success criterion established for the study at Day 64 for the proportion of subjects meeting or exceeding the threshold of protection for BioThrax (primary endpoint), it is believed that a sufficiently powered study (the current study) with adequate sample size using the appropriate threshold of protection for AV7909 will evidence the desired immunogenicity response at both Day 64 and Day 29.

4.4. End of Study Definition

A participant is considered to have completed this study if he/she has completed the final safety follow-up phone contact at Month 13, eg, occurring nominally 12 months after the last vaccination. Participants who do not complete the Month 13 phone contact 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 on-study-participant's final safety follow-up call at Month 13, or earlier if the participant's last follow-up contact occurs before this time point.

5. STUDY POPULATION

Participants will be recruited at approximately 40 clinical research sites in the US. A total of 3850 healthy adults meeting the eligibility criteria will be randomized to one of the four treatment groups.

No waivers of inclusion and/or exclusion criteria will be permitted in the trial. Racial distribution will be monitored among recruited participants.

5.1. Inclusion Criteria

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

1. Written informed consent obtained from the participant (dated and signed).
2. Healthy condition as established by medical history and clinical examination before entering into the study.
3. A male or female aged 18 to 65 years, inclusive, at the time of informed consent.
4. Body mass index (BMI) $\leq$35.0 kg/m^2 at Screening visit.
5. Have adequate venous access for phlebotomies.
6. For a woman of childbearing potential (WOCBP), negative serum pregnancy test at Screening and negative urine pregnancy test prevaccination on Day 1, not currently breastfeeding, and no intention to become pregnant during the study through Month 13

   Every female participant is considered to be a WOCBP unless surgically sterile (bilateral oophorectomy or bilateral salpingectomy or hysterectomy) OR postmenopausal (defined as >12 consecutive months without menses and screening follicle-stimulating hormone [FSH] >30 mIU/mL). Women who are not of childbearing potential are allowed to enroll if they are surgically sterile or postmenopausal as defined above.

5.2. Exclusion Criteria

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

1. Use of any investigational or nonregistered product (drug, vaccine, device, or combination product) within 30 days preceding the dose of study vaccine, or planned use during the study through Month 13.
2. Positive test 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.
3. Chronic administration (defined as >14 days) of immunosuppressants or other immune-modifying drugs (includes oral or parenteral corticosteroids, eg, a glucocorticoid dose exceeding 10 mg/day prednisone or equivalent) within six months prior to the vaccine dose; inhalation use (eg, for seasonal allergies) is permitted.
4. Planned administration of any commercially-available vaccine from seven days prior to the first study vaccination through two weeks after the last vaccination.

5. 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), or latex.
6. History of anthrax disease, suspected exposure to anthrax, or previous vaccination with any anthrax vaccine.
7. Have a tattoo/scar/birthmark or any other skin condition affecting the deltoid area that may interfere with injection site assessments.
8. A positive blood test for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) HIV-1 or HIV-2 antibodies.
9. Any confirmed or suspected immunodeficiency condition (congenital or secondary) or autoimmune disease based on medical history and PE, eg, Guillain-Barré.
10. A family history of congenital or hereditary immunodeficiency.
11. Major congenital defects or serious chronic illness, including any cancer other than the following: a) any non-metastatic cancer (excluding hematologic malignancies) or melanoma of which the participant has been disease-free for at least five years and b) localized skin cancer, resected (including squamous cell and basal cell carcinomas).
12. 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.
13. Any medical condition that, in the opinion of the investigator, could adversely impact the participant's participation or the conduct of the study.
14. Any planned elective surgery during the study through 12 months after the last vaccination.
15. Planned 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 phone contact.
16. Woman of childbearing potential refusing to practice an adequate method of contraception from at least one month before Day 1 and continuing through Month 13.

    An adequate method of contraception is defined as abstinence from sexual intercourse; prior bilateral tubal ligation; monogamous relationship with a vasectomized partner (vasectomy performed at least six months prior to the participant's screening visit); or any of these forms of birth control: pill, intrauterine device (IUD), implantable or injectable contraceptive (eg, Norplant® or Depo-Provera®), removable device (eg, NuvaRing® or Evra® patch), or double-barrier method (condom with spermicide, diaphragm with spermicide). The PI and/or designee will discuss with the participant the need to use adequate contraception consistently and correctly and document such conversation in the participant's chart. In addition, the PI and/or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

17. Member or family member of the investigator site team.
18. Previously served in the military any time after 1990 and/or plan to enlist in the military at any time from screening through the final telephone contact.

5.3. Lifestyle Restrictions

Not applicable.

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 on 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 and receive their first vaccination. The results of clinical laboratory tests at Screening (if not otherwise specified in the inclusion/exclusion criteria) should be within the central laboratory's reference ranges or, if outside such ranges, be assessed by the investigator as not clinically significant. During the initial Screening visit, the PI or designee will confirm, by documentation of the evaluation, any transient acute condition that may affect the participant's Screening clinical laboratory results. 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.

6. TREATMENTS

6.1. Treatment Administration

6.1.1. Treatment Description

6.1.1.1. AV7909

AV7909 is a preformulated, sterile, milky-white suspension for IM injection consisting of the AVA bulk drug substance and CPG 7909 adjuvant. Participants in Groups 1, 2, and 3 will each receive one dose of AV7909 0.5 mL IM, consisting of 0.5 mL AVA and 0.25 mg CPG 7909, on Day 1 and one dose IM on Day 15. Each group will receive a specific lot of AV7909, for a total of three AV7909 lots tested in Groups 1 to 3.

The AV7909 vaccine, manufactured by Emergent BioDefense Operations Lansing LLC (Lansing, MI), 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.

6.1.1.2. BioThrax

BioThrax AVA is a sterile, milky white suspension made from cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *B. anthracis*. Participants in Group 4 will receive one 0.5 mL dose of AVA SC on Day 1, on Day 15, and on Day 29.

Commercial BioThrax, manufactured by Emergent BioDefense Operations Lansing LLC (Lansing, MI), will be supplied in 5 mL multi-dose vials (10 doses per vial). For the purposes of this trial, only a single dose (0.5 mL) will be used from each vial.

The BioThrax product label used will be the current commercial label.

6.1.1.3. Placebo

Sterile, preservative-free saline for injection (0.9% NaCl) USP provided in 10 mL single-use vials will be used for the saline placebo dose. Participants in Group 1, Group 2, and Group 3 will each receive one dose (0.5 mL) of placebo SC on Day 29 for masking purposes. For the purposes of this trial, only a single dose (0.5 mL) will be used from each vial.

A copy of the product label can be found in the Pharmacy Manual.

6.1.2. Dosing and Administration

The dosing schedule for each treatment group is presented in Table 3.

Table 3: Dosing Schedule

Group Number/Treatment	Days 1 and 15	Day 29
1/AV7909 Lot 1	0.5 mL AV7909 IM	0.5 mL placebo SC
2/AV7909 Lot 2	0.5 mL AV7909 IM	0.5 mL placebo SC
3/AV7909 Lot 3	0.5 mL AV7909 IM	0.5 mL placebo SC
4/BioThrax	0.5 mL BioThrax SC	0.5 mL BioThrax SC

IM = intramuscular; SC = subcutaneous.
AV7909=0.5 mL AVA + 0.25 mg CPG 7909. Placebo=saline for injection.

All vaccinations will be administered in the clinic by authorized unblinded personnel following a complete or symptom-directed PE and (in WOCBP only) urine pregnancy test. If a participant has any condition that, in the opinion of the PI or designee, would render vaccination unsafe for that individual (eg, febrile illness, pregnancy) or would interfere with evaluations, then the vaccination will be rescheduled (if the condition is likely to resolve and the rescheduled vaccination visit will still occur within the visit window; refer to Section 8.1) or discontinued (refer to Section 7.3.1). Participants who fail for any reason to receive their first vaccination on the day of randomization will be withdrawn from the study and will be considered ineligible for study rescreening. Participants who fail to receive their second vaccination within the allowed visit window or for whom scheduling or other conflict precludes receipt of the third vaccination within the allowed visit window will be discontinued from further vaccinations. All vaccinated participants (regardless of number of injections) will continue to participate in the trial for all subsequent safety visits and follow-up phone calls.

Vaccinations will be administered in alternating arms (when possible) for each injection. For example, if the Day 1 injection is administered to the left arm, it is recommended that the Day 15 injection be administered to the right arm, and Day 29 injection be administered to the left arm. Using the same arm for subsequent vaccination(s) if necessary, may occur only in a case when the other arm is not available for vaccination and only if any sign(s) or symptom(s) of a prior injection have been resolved. The arm used for each injection must be recorded in the source documents and eCRF.

Vaccinations will be administered by unblinded personnel (eg, unblinded pharmacist) who are licensed to administer medication/vaccination and will not be involved in any other study activity involving participant contact or assessment. Only the deltoid muscle will be used for IM injection of investigational product (IP). The SC injection of IP will occur only over the deltoid region. Injections given IM should be made on the thickest and central portion of the deltoid muscle.

The IP will be administered as follows:

1. The IP will not be mixed with any other product in the syringe.
2. To avoid inadvertent unblinding, the injection will be administered in a segregated area of the clinical site ensuring the IP prepared for administration is kept apart from blinded site personnel. As a measure to maintain blind conditions for the participant, the syringe barrel will be masked to obscure the contents (refer to Section 6.2.3). The participant will

be instructed to look away from the syringe as the participant is prepared for vaccination and as the injection is administered.

3. The area of skin to be injected will be wiped with an alcohol swab or other suitable antiseptic and allowed to dry.
4. For the IM injections, holding the needle at a 90° angle to the skin, IP will be injected into the deltoid muscle. The IP WILL NOT be injected intravenously (IV) or intra-arterially. The usual precautions will be followed to ensure that a blood vessel has not been entered before injection of the IP.
5. For the SC injections, holding the needle at a 45° angle to the skin, the IP will be injected subcutaneously over the deltoid region. The IP WILL NOT be injected IV or intra-arterially. The usual precautions will be followed to ensure that a blood vessel has not been entered before injection of the IP.
6. After injection, the needle will be withdrawn and disposed of as per institutional regulations.
7. The injection site will be briefly and gently massaged to promote dispersal of the IP.

After each vaccination by the unblinded member of site staff, the participant will be observed for at least 30 minutes (by a blinded member of site staff) for any adverse effects of vaccination, especially anaphylactic reactions. Site personnel will be trained in the recognition of early symptoms of anaphylactic reactions, a rare but potentially serious reaction to parenteral injections. Any such reactions must be reported as AEs (refer to Section 9). Sites must be ready to treat participants experiencing clinically significant dyspnea or hypotension, wheezing, or generalized urticarial reactions. Appropriate medical therapy for anaphylaxis will be administered, if indicated, including IM or SC epinephrine 1:1000, corticosteroids, diphenhydramine, bronchodilators, IV volume expansion, and/or oxygen. Participants will be evaluated and carefully monitored until complete resolution of any signs and symptoms, if they occur, to include transfer to the nearest emergency room if required.

For more detailed instruction on IP administration, refer to the Pharmacy Manual.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Acquisition

AV7909 and BioThrax liquid suspension for injection and saline placebo will be shipped to investigational sites from the drug depot following approval by the institutional review board/independent ethics committee (IRB/IEC) and Emergent. All AV7909 and BioThrax shipments will be accompanied by TempTale® temperature monitors to record any excursions outside of required storage conditions of 2-8 °C (36-46 °F). Detailed instructions for inventory receipt, temperature excursions, and IP resupply are provided in the Pharmacy Manual.

6.2.2. Product Storage and Stability

Investigational products will be secured and accessible only by unblinded study personnel authorized by the PI. AV7909 and BioThrax will be stored at the investigational site in a

designated, restricted-access refrigerator maintained within the required storage conditions of 2-8 °C (36-46 °F). The vials will not be frozen. In order to guarantee proper storage conditions, the minimum, actual and maximum temperature in the storage refrigerator will be continuously monitored for correct temperature. A back-up power source for the refrigerator is required.

Investigational products that are suspected of loss of cold chain, whether during shipping or at the investigational site, will be immediately quarantined and not used until further notice. The site will refer to the Pharmacy Manual and contact the unblinded contract research organization (CRO) study monitor for further instruction.

After a single dose is withdrawn from either AV7909 or BioThrax vials for administration to a participant, the vial will thereafter be maintained at room temperature pending final drug accountability procedures.

Saline placebo is to be stored at room temperature (20-25 °C; 68-77 °F) before and after use.

6.2.3. Preparation of Investigational Product for Injection

Vaccine doses must not be drawn into a syringe until immediately before administration. Pre-filling of the syringes is discouraged because of the potential for administration errors. In addition, the stability of the vaccine stored in the syringes has not been determined. An unblinded study pharmacist or other designated, licensed study personnel will prepare each syringe of vaccine or placebo according to the following instructions in a segregated area of the clinical site ensuring the IP prepared for administration is kept apart from blinded site personnel:

1. A separate 1”- or 1½” 23- or 25-gauge sterile needle and 1.0 mL syringe will be used for each participant.
2. The IP (AV7909, BioThrax, and placebo) will be gently rolled between the hands to ensure that the suspension is homogeneous and visually inspected for particulate matter and discoloration prior to preparing the syringe. If the product appears discolored or has visible particulate matter, the vial must not be used – THE VIAL MUST BE QUARANTINED and retained for collection by the CRO study monitor or Sponsor representative.
3. The rubber stopper will be wiped with an alcohol swab and allowed to air dry before inserting the needle. The IP will be drawn into a sterile 1.0 mL syringe for administration. The volume and contents of the syringe will be verified by a second unblinded person before administration.
4. The syringe barrel will be masked to obscure the contents. This masking must not cover the syringe hub, to allow for observation of any blood return during administration.
5. The vial will be resealed and covered with tamper-evident tape to indicate no additional doses may be withdrawn (applies to the AV7909 and BioThrax multi-dose vials).

6.2.4. Accountability

Authorized, unblinded pharmacy personnel will maintain accurate records of receipt of AV7909, BioThrax, and saline placebo used for the study, including dates of receipt and TempTale records. In addition, accurate records will be kept regarding when and how much of each IP is

dispensed and used for each participant in the study. All accountability procedures will be maintained throughout the duration of the study, as detailed in the Pharmacy Manual.

No vials of AV7909, BioThrax, or saline placebo, including empty, damaged or partially used ones, are to be discarded by the investigator site. Once vaccinations are completed, in order to satisfy regulatory requirements regarding drug accountability, the unblinded CRO study monitor will reconcile all vials of study product, used and unused, according to applicable state and federal regulations and destroy per Emergent instructions.

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 Day 1 (randomization) visit, after the PI has confirmed that the participant meets all of the inclusion criteria and none of the exclusion criteria, the participant will be randomized to a treatment group via an interactive voice and/or web response system (IxRS). The randomization plan will describe the method of treatment allocation and implementation of this method in the IxRS. This plan will be prepared by a statistician and finalized prior to randomization of the first participant. Randomization will be stratified by site.

If a participant signs an ICF but is never randomized, the participant is considered to be a screen failure (refer to Section 5.4).

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

6.3.2. Blinding

The site pharmacists or other designated, licensed study personnel who will prepare and/or administer the vaccinations will be unblinded to IP assignment. These individuals must be licensed to administer medication/vaccination and will not be involved with participant evaluations, nor will they engage in other study activities that could reveal the blind or introduce bias in the study data.

Principal investigators (PIs), all investigational site staff (except those responsible for preparing/administering the IP), representatives of the Sponsor (except unblinded study monitor[s] and unblinded Quality Assurance representative[s]), representatives of Biomedical Advanced Research and Development Authority (BARDA), CRO staff (except unblinded

statistician and unblinded study monitor[s]), and all participants enrolled in this study will be blinded to the IP assignment. To facilitate study oversight while preserving the study blind, a minimum number of CRO and Sponsor personnel will have access to treatment randomization information. The unblinded CRO statistician will have access to the treatment assignment information in the IxRS to support the activities of the DSMB. During monitoring visits, an unblinded CRO study monitor will check that the blind has been maintained properly and will review IP accountability records. Oversight of this activity will be facilitated by the Sponsor's unblinded study monitor(s). Blinded CRO study monitors will continuously assess the progress of the study, but not have access to the unblinded pharmacy records. Individuals with access to the treatment assignment details will not share the identifying information with blinded personnel while the study blind is in effect.

Under certain circumstances (eg, safety reasons, required reporting to regulatory agencies), unblinding of IP for a particular participant will be allowed. Otherwise, unblinding of the study will only occur after the clinical database has been locked. Refer to Section 9.5 for procedures on how to break the blind for individual participants or procedures in case of accidental participant unblinding. Refer to the Pharmacy Manual for procedures in case of accidental unblinding of study-affiliated personnel (Sponsor, CRO, BARDA).

6.4. Treatment Compliance

The IP will be administered to the subject by the unblinded investigational site staff in a controlled, clinical environment. The date and time of the vaccine administration will be recorded on the source documents and eCRF.

6.5. Concomitant Therapy

Medication usage will be collected from participants and recorded in the participant's source documents and eCRF at Screening and at each study visit up through Day 64/EWV. After Day 64, medication usage will be recorded in the eCRF if involving an AE, SAE or AESI. Prior medications are those used from within 30 days before Screening through the time of the first vaccination, while concomitant medications are those used after the first vaccination. The medication name, dose, route, frequency, indication, and stop and start days/times for each new medication will be recorded. Refer to Section 5.2 for prior medication usage that is disqualifying for study participation.

Prohibited and restricted concomitant medications during the study, which include anti-inflammatory or antipyretic medications, vaccines, immunomodulatory agents, antineoplastic agents, and immunoglobulins/other blood products, are summarized in Table 4. The MM should be consulted for any questions about prohibited or restricted medication usage.

Table 4: Prohibited and Restricted Concomitant Medications

Type[a]	Examples[b]
Anti-inflammatory or antipyretic medication: prohibited within 24 hours before or after vaccination	Aspirin-containing medication, NSAIDs, acetaminophen-containing medication
Any commercially-available vaccine through two weeks after the last vaccination	BCG Vaccine, Engerix-B, Havrix, HEPLISAV-B, Imovax, influenza vaccines, Ixiaro, JE-Vax, Menomune-A/C/Y/W-135, Prevnar 13, Recombivax HB, Twinrix, Vaxchora, Vaqta
Immunomodulatory agents through Month 13 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 Azasan (Salix Pharmaceuticals), CellCept (Roche Laboratories), Gengraf (Abbott), MICRhoGAM ultra-filtered (Ortho-Clinical), Myfortic (Novartis), Neoral (Novartis), Orthoclone OKT3 sterile solution (Ortho Biotech), Prograf (Fujisawa), Rapamune (Wyeth), Rituximab (Rituran, Mabthera; Genentech), Sandimmune (Novartis), Simulect (Novartis), Thymoglobulin (SangStat Medical Corp.), Zenapax (Roche Laboratories)
Antineoplastic agents through Month 13	Cyclophosphamides (Cytoxan, Neospar), Cytarabine (Cytosar-U, Ara-C, Cytosine arabinoside), Depocyt (Enzon), methotrexate, vincristine (Oncovin, Vincasar)
Immunoglobulins and/or any blood products through Month 13	Anthrasil, Bivigam, Carimune NF Nanofiltered, CUVITRU, Flebogamma DIF 5% & 10%, GamaSTAN S/D, Gammagard, Gammaplex 5% & 10%, Gamunex-C, HepaGam B, Hizentra, HYQVIA, OCTAGAM, Privigen, VARIZIG
Any investigational or nonregistered product (drug, vaccine, device, or combination product) through Month 13	-

MM=Medical Monitor; NSAID = non-steroidal anti-inflammatory drug.
[a]Refer to Section 5.2 for prior medication usage that is disqualifying for study participation.
[b]Example medications are provided for reference – this is not meant to be an exhaustive list. Consult with the MM as needed.

The use of pain/fever medications recorded in participant e-diaries will be reviewed by investigational site staff during routine monitoring of e-diary entries (refer to Section 8.3.5.1) and, for completeness of the concomitant medication record, must also be added to the eCRF.

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:

- >3% of participants having the same Grade 3 or higher AE
- 3 suspected unexpected serious adverse reactions (SUSARs) within the same body system as assessed by the Sponsor
- 5 potential AESIs considered related to the IP, as assessed by the Sponsor
- single AESI considered related to the IP, as assessed by the DSMB

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 8.4.1).

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.

A 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 Subject

All participants have the right to withdraw at any time during the study without prejudice. The PI can also discontinue an individual's participation in the 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 Month 13 providing they have received at least one vaccination. Participants who discontinue treatment prematurely for any reason after receiving the first vaccination will be encouraged to continue in the study for any remaining study visits (for safety assessments only) and the safety follow-up phone calls at Day 43 and Months 4, 7, 10, and 13.

If a participant discontinues vaccinations and/or participation in the study, the reason(s) must be fully evaluated and recorded appropriately in source documents and eCRFs. Reason for discontinuation of vaccination 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 vaccination discontinuation and/or study withdrawal.

7.3.1. Discontinuation of Vaccination

Vaccinations will be permanently discontinued in participants who meet the individual participant halting rules in Table 5. The date and reason for discontinuation of vaccination is to be recorded on the eCRF.

Participants who have received at least one vaccination will be encouraged to participate in all remaining study visits (for safety assessments only) and safety follow-up calls through Month 13. A participant who complies with safety-only assessments after prematurely discontinuing vaccinations will be considered to be continuing in the study. Participants who are being followed for safety only will not be required to have any further TNA blood draws and assessments associated with vaccination (eg, vital signs evaluation occurring 30 ± 5 minutes after vaccination and e-diary). However, e-diary entries associated with a past vaccination and site review of those entries must still be completed (refer to Section 8.3.5.1).

If a participant who has received at least one vaccination discontinues treatment prematurely but refuses to continue with safety-only follow up, the participant must be withdrawn from the study, with the reason for study withdrawal recorded on the eCRF (refer to Section 7.3.2). If the refusal to participate in safety-only follow-up procedures occurs before Day 64, the participant will be requested to attend an EWV for a final in-clinic safety assessment before being withdrawn from the study (refer to EWV procedures under Section 8.1.7).

Table 5: Criteria for Discontinuation of Vaccination for Individual Participants

No.	Item
1.	Grade 2 or greater hypersensitivity believed by the PI to be related to the vaccine, eg, anaphylaxis, allergic reaction
2.	Any Grade 3 or higher systemic reactogenicity symptom assessed by e-diary and confirmed by the PI
3.	Any AE that would pose a risk to the participant as determined by the PI if continued vaccinations were to occur
4.	Any violation of eligibility criteria discovered after randomization that would pose a risk to the participant, as determined by the PI and agreed by the MM
5.	Febrile illness (fever > 100.4 °F) within three days prior to any vaccination (Exception: The vaccination visit may be rescheduled to another day outside this three-day period providing it will not fall outside the required visit window for the visit [refer to Section 8.1].)
6.	Receipt of IP associated with loss of cold chain
7.	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 vaccination visit may be rescheduled to another day providing it will not fall outside the required visit window for the visit [refer to Section 8.1].)
8.	Scheduling or other conflict results in a vaccination visit falling outside the required window (± 1 day for Day 15; ± 2 days for Day 29)
9.	Received prohibited medication, as determined by the PI and agreed by the MM
10.	Causally related Grade 3 or higher unsolicited AE as assessed by the PI[a]
11.	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.

7.3.2. Withdrawal from Study

Reasons for withdrawal of individual participants from the study prior to the Month 13 final safety follow-up phone call are to be recorded on the eCRF. The reason for withdrawal from the study will be recorded as one of the following:

1. Occurrence of any AE which, in the opinion of the PI or designee, warrants the participant's permanent withdrawal from the trial (medical circumstances permitting, the participant will be encouraged to continue in the study for safety-only follow-up; refer to Section 7.3.1).
2. Death
3. Lost to follow-up (see Section 7.4)
4. Noncompliance with study drug
5. Physician decision
6. Withdrawal (of consent) by the participant
7. Other (specify reason)

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.

The PI will notify Emergent promptly when a participant is withdrawn from the study. Before a participant who has received at least one vaccination is withdrawn from the study, the participant will be encouraged to comply with safety-only follow up procedures for the remaining study duration through Month 13 (refer to Section 7.3.1). An EWV will be requested of any participant who has received at least one vaccination but is withdrawn from the study before in-clinic visit Day 64 (refer to Section 8.1.7 for EWV procedures).

7.4. Lost to Follow-up

Participants who cannot be contacted during the in-clinic evaluation period through Day 64 or at the Month 13 safety follow-up phone call 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 withdrawal in the eCRF. The site will make three attempts to contact the participant by telephone, with contact attempts spaced at least one week apart. 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.

Refer to Section 8.1.8 for procedures when participants cannot be contacted at the Months 4, 7, and 10 safety follow-up phone calls.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Schedule of Assessments

Individual participation in this study from the first visit to last visit inclusive of safety follow-up phone contacts will be approximately 15 months. Screening will be approximately one month (Day -28 to Day -2) followed by four in-clinic visits occurring over 2 months (9 weeks). Safety follow-up phone calls will be conducted at Day 43 and Months 4, 7, 10 and 13. The following sections also provide detailed lists of assessments to be performed by visit.

Of note, collection of the blood sample for immunogenicity assessments on vaccination days must be completed before the vaccine is administered.

A Schedule of Assessments is provided in Table 6, in which visit windows are specified (eg, ± 1 day, meaning one day before or after the target visit day will be allowed).

A licensed physician will be identified as the PI for the site. The PI will designate appropriately qualified staff members to perform study tasks and procedures, including preparation and administration of the IP. Assessments of AEs and eligibility criteria may only be made by those with the medical training and authority to make a diagnosis. All task delegates will be recorded in the Delegation of Authority Log maintained at the investigational site.

Note: all study procedures/assessments outlined in Section 8.1 below will be performed by blinded member(s) of site staff, except where noted otherwise [eg, unblinded member(s) of site staff will prepare and administer the IP].

Table 6: Schedule of Assessments

Study Periods	**Screen-ing**	**In-clinic Visits**					**Safety Follow-up Phone Calls**	**Unscheduled Visit**	**Comments**
Study Day (Visit Window in Days)	**-28 to -2**	**1**	**15 (±1)**	**29 (±2)**	**64 (±3)**	**EWV**	**43 (±2), 120 (±14), 211 (±14), 302 (±14), 394 (±14)**	-	On unscheduled visit days: $X_{<D64}$ = assessment to be performed only if before Day 64.
Sign and date ICF	X								-
Subject ID assigned	X								-
Demographics	X								-
Medical history	X	X							Any current signs and symptoms assessed as trial-procedure-related will be recorded as AEs, otherwise recorded as medical history.
Vital signs: systolic and diastolic blood pressure (sitting), heart rate, respiratory rate, and temperature	X	X	X	X	X	X		$X_{<D64}$	On vaccination days, vital signs will be taken before vaccination and at 30 minutes (± 5 min) postvaccination.
Vital signs: height and weight	X								-
Medication usage	X	X	X	X	X	X	X	X	Medications taken within 30 days prior to the Screening visit or since the last visit (including unscheduled visit) through Day 64/EWV will be recorded. Additionally, medication use will be recorded at the time of the safety follow-up phone calls (also during unscheduled visits following safety phone calls) only for those subjects who report an AE, SAE or AESI.

Study Periods	**Screen-ing**	**In-clinic Visits**					**Safety Follow-up Phone Calls**	**Unscheduled Visit**	**Comments**
Study Day (Visit Window in Days)	**-28 to -2**	**1**	**15 (±1)**	**29 (±2)**	**64 (±3)**	**EWV**	**43 (±2), 120 (±14), 211 (±14), 302 (±14), 394 (±14)**	-	On unscheduled visit days: $X_{<D64}$ = assessment to be performed only if before Day 64.
Complete PE	X				X	X			Abnormal findings are to be recorded as AEs after Day 1 postvaccination if new or increased in severity unless the PE abnormality is part of a symptom complex that is already reported as an AE.
Viral serology testing	X								Testing for HIV-1 or HIV-2 antibodies, hepatitis B surface antigen, and hepatitis C antibody.
Use of adequate method of contraception (WOCBP only)	X	X	X	X	X	X	X	X	The preferred method of adequate contraception as defined in Section 5.2 will be documented in the WOCBP's chart and reviewed for continued use at every visit or contact thereafter.
FSH	X								Performed to confirm postmenopausal status only in women having >12 consecutive months without menses.
Hematology	X			X		X			Any Grade 3 neutropenia or lymphopenia will be evaluated with an unscheduled repeat CBC approximately 72 hours after the initial specimen was drawn, unless a protocol-scheduled CBC has already shown resolution to Grade 1 or lesser toxicity. EWV will include hematology testing only if the visit occurs before Day 29.
Serum chemistry	X			X		X			EWV will include serum chemistry testing only if the visit occurs before Day 29.

Study Periods	**Screen-ing**	**In-clinic Visits**					**Safety Follow-up Phone Calls**	**Unscheduled Visit**	**Comments**
Study Day (Visit Window in Days)	**-28 to -2**	**1**	**15 (±1)**	**29 (±2)**	**64 (±3)**	**EWV**	**43 (±2), 120 (±14), 211 (±14), 302 (±14), 394 (±14)**	-	On unscheduled visit days: $X_{<D64}$ = assessment to be performed only if before Day 64.
Urinalysis	X			X		X			EWV will include urinalysis testing only if the visit occurs before Day 29.
Urine drug screening	X								Participants with any positive test result may not be randomized.
Pregnancy test: serum	X				X	X			Performed for all WOCBP including, at Screening only, women suspected to be postmenopausal. Exempt from pregnancy testing: women confirmed to be surgically sterile and confirmed to be postmenopausal after the Screening FSH test result is known. If the urine pregnancy test is positive, serum testing will be performed. Urine pregnancy test results will be captured in the eCRF.
Pregnancy test: urine		X	X	X					
Study eligibility	X	X							-
Continuing eligibility for vaccination			X	X					If a participant has any condition that, in the opinion of the PI or designee, would render vaccination unsafe for the participant (eg, febrile illness, pregnancy) or would interfere with evaluations, then the vaccination will be rescheduled (if the condition is likely to resolve and the rescheduled vaccination visit will still occur within the visit window) or discontinued.

Study Periods	**Screen-ing**	**In-clinic Visits**					**Safety Follow-up Phone Calls**	**Unscheduled Visit**	**Comments**
Study Day (Visit Window in Days)	**-28 to -2**	**1**	**15 (±1)**	**29 (±2)**	**64 (±3)**	**EWV**	**43 (±2), 120 (±14), 211 (±14), 302 (±14), 394 (±14)**	-	On unscheduled visit days: $X_{<D64}$ = assessment to be performed only if before Day 64.
Symptom-directed PE		X	X	X				$X_{<D64}$	Symptom-directed PEs are to be conducted prior to vaccination on vaccination days. Abnormal findings are to be recorded as AEs after Day 1 postvaccination if new or increased in severity unless the PE abnormality is part of a symptom complex that is already reported as an AE.
Immunogenicity (TNA) testing		X		X	X	X			Blood for determination of TNA will be collected from participants before vaccination on days when injections are scheduled. A sample will be collected at the EWV only if within the visit window for Day 64.
Auto-antibody testing and thyroid-stimulating hormone (TSH) assessment		X			X	X		X	Blood samples will be collected for testing of RF, ANA and anti-dsDNA antibodies and TSH. The Day 1 samples are collected predose. A blood sample for auto-antibody testing will be collected at an unscheduled visit from participants reporting a potential AESI. A sample for TSH assessment will be collected at unscheduled visit(s) as per the investigator's discretion (ie, report of potential AESI).
Randomization of eligible participants		X							-

Study Periods	**Screen-ing**	**In-clinic Visits**					**Safety Follow-up Phone Calls**	**Unscheduled Visit**	**Comments**
Study Day (Visit Window in Days)	**-28 to -2**	**1**	**15 (±1)**	**29 (±2)**	**64 (±3)**	**EWV**	**43 (±2), 120 (±14), 211 (±14), 302 (±14), 394 (±14)**	-	On unscheduled visit days: $X_{<D64}$ = assessment to be performed only if before Day 64.
Vaccination		X	X	X					IP will be prepared by an unblinded member of site staff on Day 1. Participants will be vaccinated (by an unblinded member of site staff) as assigned by randomization on Day 1, followed by 30-minute observation (by a blinded member of site staff) for adverse effects of vaccination especially anaphylaxis.
Provision and instructions on use of the following: hand-held device, oral thermometer and injection site reaction measurement tool		X							A hand-held device will be provided only to those participants who do not have or do not wish to use their own personal device. Instructions on use of hand-held device, oral thermometer and injection site reaction measurement tool will be provided on Day 1 post-vaccination.
Participant e-diary entry		X→	→X→	X→					E-diary completion instructions and training will be provided on Day 1. Subjects will be instructed to complete the e-diary starting on the evening of Day 1 (with Day 1 being the day of first vaccination) and on every subsequent evening (for at least seven days). Participants are to complete the e-diary 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.

Study Periods	**Screen-ing**	**In-clinic Visits**					**Safety Follow-up Phone Calls**	**Unscheduled Visit**	**Comments**
Study Day (Visit Window in Days)	**-28 to -2**	**1**	**15 (±1)**	**29 (±2)**	**64 (±3)**	**EWV**	**43 (±2), 120 (±14), 211 (±14), 302 (±14), 394 (±14)**	-	On unscheduled visit days: $X_{<D64}$ = assessment to be performed only if before Day 64.
E-diary review by PI/site staff			→X	→X→		X	X (Day 43 only)	$X_{<D64}$	Site staff will assess e-diary data daily and review it with participants at the Day 15 and 29 visits, as well as at unscheduled visits occurring before Day 64 and EWV if applicable. On Day 43 (±2 days), site staff will follow-up with a telephone call to review e-diary data entered by the participant after Day 29.
Collect hand-held device					X	X			The hand-held device will be collected from any applicable participants who did not already return it using the provided return packaging.
AEs	X	X	X	X	X	X	X	X	AEs will be followed until resolution, stabilization, or referral. From the signing of the ICF at the Screening visit until the first vaccination on Day 1, signs or symptoms resulting from trial-related procedures only will be recorded as AEs on the AE eCRF; all others reported in this time period will be recorded on the Medical History eCRF.
SAEs/potential AESIs		X	X	X	X	X	X	X	A list of AESIs is provided in Appendix B.

AE = adverse event; AESI = adverse event of special interest, eg, AE potentially associated with autoimmune disease as defined by CBER and might represent a safety signal for vaccine-associated autoimmunity; ALT = alanine aminotransferase; BUN = blood urea nitrogen; ANA = antinuclear antibody; AST = aspartate aminotransferase; CBC = complete blood cell count; dsDNA = double-stranded deoxyribonucleic acid; EWV = early withdrawal visit; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; ID = identification; NA = not applicable; PE = physical examination; RBC = red blood cell; RF = rheumatoid factor; SAE = serious adverse event; TNA = toxin neutralizing antibody; WBC = white blood cell; WOCBP = women of childbearing potential
EWV procedures are to be performed for participants who withdraw from the study before Day 64.
Safety follow-up phone calls occur at Day 43, Months 4, 7, 10, and 13 (nominally 0.5, 3, 6, 9, and 12 months after the last vaccination).

8.1.1. 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 starts once the ICF is signed and dated. The following activities will occur during the Screening visit or period:

- Ensure review and completion of all required information on the ICF and capture in site source documentation
- Assign the subject ID number
- Record demographics
- Record medical history including current signs and symptoms, which will be recorded as AEs only if they result from a study-related procedure(s)
- (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
- Conduct complete PE
- Assess vital signs and height and weight
- Record medications taken within the last 30 days
- Collect blood sample for:
  - Viral serology (human immunodeficiency virus [HIV] antibodies, hepatitis B surface antigen [HBsAg], and hepatitis C antibody)
  - FSH (performed to confirm postmenopausal status only in women having >12 consecutive months without menses)
  - Hematology
  - Serum chemistry
  - Serum pregnancy test (women only, exempting women who are documented to be surgically sterile; refer to Section 5.1)
- Collect urine sample for:
  - Urinalysis
  - Urine drug screening
- Review for study eligibility against inclusion/exclusion criteria, to include a review of all safety and screening laboratory results (based on the central laboratory's reference ranges, or if outside the ranges, based on the investigator's assessment of clinical significance) once available

8.1.2. Day 1 (Randomization, Day of First Vaccination)

The following will occur on Day 1 prior to vaccination:

- Update medical history including signs and symptoms, which will be recorded as AEs only if the event results from a study-related procedure
- Assess vital signs
- Conduct symptom-directed PE
- Record medications taken since the last visit
- Collect blood samples for:
  - TNA testing
  - RF, ANA and anti-dsDNA antibodies testing
  - TSH assessment
- 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 negative confirmatory 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 [refer to Section 5.4])
- Review for study eligibility against inclusion/exclusion criteria, to include a review of all safety and screening laboratory test results (based on the central laboratory's reference ranges, or if outside the ranges, based on the investigator's assessment of clinical significance) and status of ongoing AEs since the prior visit
- Randomize eligible participants

The participant will be vaccinated (by an unblinded member of site staff) as per the randomization group assignment.

The following will occur after vaccination [as performed by blinded member(s) of site staff]:

- Monitor participants for at least 30 minutes postvaccination for adverse effects of vaccination, especially anaphylaxis
- Assess vital signs at 30 ± 5 minutes postvaccination
- Provide hand-held device to those participants requiring one to access the web-enabled e-diary, eg, participant does not have or does not wish to use own personal device; pre-paid return packaging will be provided with the device, to enable the participant to mail the device at the conclusion of all e-diary entries
- Instruct participant on use of the e-diary/provided hand-held device
  - E-diary is to be completed starting on the evening of Day 1 (the day of first vaccination) and on every subsequent evening (for at least seven days). Participants are to complete the e-diary 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.

- Provide an oral thermometer and injection site reaction measuring tool and instruct the participant on their use
- Assess the participant for AEs, SAEs, and AESIs

8.1.3. Day 15 ± 1 day (Day of Second Vaccination)

The following will occur on Day 15 ± 1 day prior to vaccination:

- Assess vital signs
- Record medications taken since the last visit
- Confirm continued use of an adequate method of contraception and collect urine sample for pregnancy test for WOCBP (if positive, a confirmatory serum pregnancy test is required)
- Conduct symptom-directed PE
- Assess the participant for AEs, SAEs, and AESIs, including review the status of ongoing AEs since the prior visit
- Review e-diary entries with the participant
- Review eligibility for continuing vaccination (refer to Section 6.1.2)

The participant will be vaccinated (by an unblinded member of site staff) as per randomization group assignment.

The following will occur after vaccination [as performed by blinded member(s) of site staff]:

- Monitor participants for at least 30 minutes postvaccination for adverse effects of vaccination, especially anaphylaxis)
- Assess vital signs at 30 ± 5 minutes postvaccination
- Assess the participant for AEs, SAEs, and AESIs

8.1.4. Day 29 ± 2 days (Day of Third Vaccination)

The following assessments will occur prior to vaccination:

- Assess vital signs
- Conduct symptom-directed PE
- Collect blood samples for:
  - TNA testing
  - Hematology
  - Serum chemistry
- Collect urine samples for:
  - Urinalysis

  - Urine pregnancy test for WOCBP (if positive, a confirmatory serum pregnancy test is required); also confirm continued use of an adequate method of contraception
- Record medications taken since the last visit
- Review e-diary entries with the participant
- Assess for AEs, SAEs, and AESIs, including review the status of ongoing AEs since the prior visit
- Review eligibility for continued vaccination (refer to Section 6.1.2)

The participant will be vaccinated (by an unblinded member of site staff) as per the randomization group assignment.

The following will occur after vaccination [as performed by blinded member(s) of site staff]:

- Monitor participants for at least 30 minutes postvaccination for adverse effects of vaccination, especially anaphylaxis)
- Assess vital signs at 30 ± 5 minutes postvaccination
- Assess for AEs, SAEs, and AESIs

8.1.5. Day 43 ± 2 days (Safety Follow-up Phone Call)

The following assessments will be performed over the phone:

- Review of e-diary and any ongoing AEs/SAEs/AESIs (if applicable)
- For WOCBP, confirm continued use of an adequate method of contraception and inquire about any possible pregnancies (refer to Section 9.3)
- Record medications taken since the last visit or contact

8.1.6. Day 64 ± 3 days (Final In-clinic Visit)

The following assessments will be performed on the Day 64 ± 3 days in-clinic visit:

- Assess vital signs
- Record medications taken since the last visit
- Perform complete PE
- Collect blood sample for:
  - TNA testing
  - RF, ANA and anti-dsDNA antibodies testing
  - TSH assessment
  - Serum pregnancy test for WOCBP; also confirm continued use of an adequate method of contraception

- Assess for AEs, SAEs, and AESIs, including review the status of ongoing AEs since the prior visit
- Collect the hand-held device used for the e-diary (if applicable), if not already returned

8.1.7. Early Withdrawal Visit

Early withdrawal visit procedures will be performed for participants receiving at least one vaccination who withdraw from the study before Day 64. The following will occur during the EWV:

- Perform complete PE
- Assess vital signs
- Collect blood samples for laboratory testing:
  - Hematology (only if the EWV occurs before Day 29)
  - Serum chemistry (only if the EWV occurs before Day 29)
  - Serum pregnancy testing for WOCBP; also confirm continued use of an adequate method of contraception
  - TNA testing (only if the sample collection is within the visit window for Day 64)
  - RF, ANA and anti-dsDNA antibodies testing
  - TSH assessment
- Collect urine sample for urinalysis (only if the EWV occurs before Day 29)
- Record medications taken since the last visit
- Assess e-diary data since the last visit, if applicable
- Assess for AEs, SAEs, and AESIs, and verify the status of ongoing, previously-reported AEs to determine if resolved
- Collect the hand-held device used for the e-diary (if applicable), if not already returned

8.1.8. Safety Follow-up Phone Calls at Month 4 ± 14 Days, Month 7 ± 14 Days, Month 10 ± 14 Days, and Month 13 ± 14 Days

All due attempts will be made to follow participants who receive at least one vaccination for safety through Month 13 (nominally 12 months after the last vaccination, presuming full compliance with the vaccination schedule), particularly for late onset autoimmune events. To mitigate loss to follow up within the year-long period, participants will be contacted by site staff at quarterly intervals. These phone contacts will be scheduled keying off the subject's actual or, if missed, target Day 29 visit (intended last vaccination day), so that all participants (even those failing to receive all three vaccinations but who are followed for safety only) are contacted at Month 4 (Day 120 ± 14 days; nominally 3 months after Day 29 final vaccination), Month 7 (Day

211 ± 14 days; nominally 6 months after Day 29 final vaccination), Month 10 (Day 302 ± 14 days; nominally 9 months after the Day 29 final vaccination), and Month 13 (Day 394 ± 14 days; nominally 12 months after the Day 29 final vaccination).

The following assessments will be performed over the phone at the Month 4, Month 7, Month 10, and Month 13 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 9.3)
- Record medications taken since the last visit or contact (if related to AE, SAE and/or AESI)
- 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 64 visit or the preceding phone contact. Any occurrence of SAE will be reported to Emergent immediately as specified under Section 9.3 and followed up per procedures described in Section 9.6.2. If an SAE has occurred, it will be recorded on the AE eCRF with any medications taken also recorded on eCRFs.

During the telephone calls, the staff member will also attempt to elicit and record in source documentation any information on AESIs 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 8.1.8) and to provide a blood sample for auto-antibody 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 9.6.2. 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 MM 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 Day 43, Months 4, 7, or 10, 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 Month 13 call are described in Section 7.4.

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 auto-antibody testing.

Unscheduled visits occurring before Day 64 will include a symptom-directed PE, measurement of vitals, AE (includes SAE/AESI) assessment inclusive of blood draw(s) for auto-antibody and/or TSH testing (if applicable), 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 64 will include an AE/SAE/AESI assessment including blood draw(s) for auto-antibody and/or TSH testing if applicable and updating of medication usage since the last visit/contact (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 9.3).

8.2. Immunogenicity/Efficacy Assessments

8.2.1. Immunogenicity Testing

Blood samples (sera) for determination of TNA titers will be collected on Day 1 and Day 29 prior to vaccination, and on Day 64. Blood samples will be collected at EWV only if it falls within the visit window for Day 64.

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 the 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 {Clement, 2008}. 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 clinical laboratory tests are specified in Table 7. 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 in WOCBP, 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 (screening laboratory test results, if not otherwise specified in the inclusion/exclusion criteria, should be within the central laboratory's reference ranges, or, if outside such ranges, be assessed by the investigator as not clinically significant) and subsequently for the continuous safety monitoring of participants. Review of the laboratory report must be documented.

The following assessments will be performed at Screening only:

- Urine drug screen (refer to Table 7 for analytes)
- 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 to confirm postmenopausal status in women having > 12 consecutive months without menses (refer to Section 5.1).

Pregnancy testing will be performed at all visits including EWV. Female participants who are confirmed at Screening to be surgically sterile (refer to Section 5.1) are exempt from pregnancy testing. A serum pregnancy test is required at Screening for all other female participants, including those suspected to be postmenopausal; any such individuals who are confirmed to be postmenopausal after the Screening FSH test result is known (refer to Section 5.1) are exempted from further pregnancy testing. Postscreening pregnancy testing in WOCBP (only) will consist of a urine pregnancy test at all visits except for a serum pregnancy test performed at Day 64 and the (if applicable) EWV. All urine pregnancy tests must be performed at the investigational site and documented to be negative on vaccination days before administration of vaccine. For participants with positive urine test results, a confirmatory serum pregnancy test will be performed. Vaccination will not be administered to any participant who tests positive for pregnancy.

Blood and urine samples for safety clinical laboratory testing (hematology, serum chemistry, urinalysis) will be collected at Screening and Day 29 and also at the EWV if the EWV occurs before Day 29. Refer to Table 7 for the complete list of analytes to be tested. Blood samples for auto-antibody assessment of RF, ANA and anti-dsDNA antibodies and TSH will be taken at Day 1 prior to vaccination, Day 64/EWV, and at the time of unscheduled visit(s) if warranted from participant report(s) of potential AESI(s) at the safety follow-up phone call(s).

Clinical laboratory results for the lab analytes that appear in Table 9 will be assigned by the central laboratory a toxicity grade (Grade 1=mild through Grade 4=potentially life-threatening)

according to the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* {CBER, 2007}. This grading – assessing severity – will aid the PI or designee in the evaluation of laboratory abnormalities and their reporting, if applicable, as AEs.

For each abnormal laboratory test result, the PI or designee needs to ascertain if this is a clinically significant change from baseline for that individual. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The PI or designee 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. Investigational sites will be alerted by the central laboratory 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 to confirm the result. The PI or designee may 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, unless a protocol-scheduled CBC has already shown resolution to Grade 1 or lesser toxicity.

If the original (retested sample) or repeat laboratory value is Grade 3 or higher, this will be considered an AE and will be recorded by the PI on the AE eCRF. Any other clinical laboratory abnormalities must also be reported as AEs if considered by the PI or designee to be a clinically significant change from baseline. As toxicity grading is being used in this study to evaluate and record AE severity (refer to Section 9.2.1), the lab toxicity grade is to be assigned as the AE toxicity grade when reporting on the AE eCRF. If the lab analyte does not have toxicity grading criteria specified in Table 9, then the PI or designee will use the grading criteria for "illness or clinical AE" in Table 8 to assign the AE toxicity grading. 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 study halting rules (see Section 7.1) and will require discontinuation of vaccinations in an individual participant if considered associated with vaccination (see Section 7.3).

Table 7: Screening/Safety Clinical Laboratory Tests

Hematology -Basophils -Eosinophils -Hematocrit -Hemoglobin -Lymphoctyes -Monocytes -Neutrophils -Platelets -RBC count -WBC count Serum Chemistry -ALP -ALT -AST -Bilirubin, Total -BUN -Creatinine -Glucose, nonfasting	Urinalysis -Appearance -Bilirubin -Color -Glucose -Ketones -Leukocyte esterase -Nitrite -Occult blood -pH -Protein -Specific gravity -Urobilinogen -Microscopic examination (only if protein, nitrite, leukocyte esterase, or occult blood results are positive) Additional Tests -FSH (only in women having > 12 consecutive months without menses to confirm postmenopausal status) -Serum/urine pregnancy test (WOCBP only; also suspected postmenopausal women at Screening only) -TSH	Viral Serology: -anti-HCV antibody -anti-HIV antibody -HBsAg Urine Drug Screen: -Amphetamines -Barbiturates -Benzodiazepines -Cannabinoids -Cocaine -Opioids Autoantibodies -RF -ANA -anti-dsDNA antibodies

ALP=alkaline phosphatase; ALT=alanine transaminase; ANA=antinuclear antibody; AST=aspartate transaminase; BUN=blood urea nitrogen; dsDNA=double stranded deoxyribonucleic acid; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; HCV= hepatitis C virus; HIV=human immunodeficiency virus; RBC=red blood cell; RF=rheumatoid factor; TSH=thyroid-stimulating hormone; WBC=white blood cell; WOCBP=woman of childbearing potential.

8.3.3. Physical Examination

The PI or appointed designee is responsible for performing the PE. Whenever possible, the same individual will perform all PEs for each participant.

A complete PE will be performed at Screening and Day 64/EWV. This examination will include a review of general appearance, head/eyes/ears/nose/throat, respiratory system, cardiovascular system, gastrointestinal system, dermatological system, lymphatic/hematological system, musculoskeletal system, neurological system, metabolic/endocrine system, and other observations. Note that a genitourinary review is not required for the PE unless clinically indicated.

Symptom-directed PEs, a targeted examination of specific body systems based on the participant's complaint(s), are to be conducted prior to vaccination on Days 1, 15, and 29 and also during unscheduled visits occurring before Day 64.

Abnormal PE findings are to be recorded as signs and symptoms on the Medical History eCRF if presenting before the vaccination on Day 1, and as AEs after Day 1 postvaccination if new or

increased in severity/frequency following vaccination. As toxicity grading is being used in this study to record AE severity (refer to Section 9.2.1), the PI or designee will assess the severity of abnormal PE findings recorded on the AE eCRF according to Table 8, which has grading options for some specific clinical symptoms, as well as a generic grading criteria for "illness or clinical AE" that will be used otherwise. Physical examination abnormalities are not to be separately reported as AEs if the PE abnormality is part of a symptom complex that is already reported as an AE. Abnormal PE findings may trigger individual participant or study halting rules (refer to Section 7).

8.3.4. Vital Signs

Vital signs including systolic and diastolic blood pressure (sitting), heart rate, respiration rate, and temperature will be obtained at Screening and each subsequent clinic visit through Day 64/EWV, including unscheduled visits occurring before Day 64. Height and weight will only be recorded at Screening. On vaccination days (Days 1, 15, and 29), vital signs will be assessed prior to vaccination and at 30 ± 5 minutes postvaccination.

The PI or designee will assess vital sign results against toxicity grade criteria (Grade 1=mild through Grade 4=potentially life-threatening) according to the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* {CBER, 2007} – refer to Table 8, with grading for oral temperature (fever), heart rate (tachycardia, bradycardia), blood pressure (hypertension, hypotension), and respiratory rate. This grading – assessing severity – will aid in the evaluation of abnormalities and their reporting, if applicable, as AEs.

Any vital sign abnormalities may be followed up with repeat testing. 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 will be reported as a Grade 3 or higher abnormality. All Grade 3 or higher vital sign abnormalities and those vital sign abnormalities determined by the PI or designee to be a clinically significant change from baseline for that participant will be recorded as AEs. As toxicity grading is being used in this study to evaluate and record AE severity (refer to Section 9.2.1), the vital sign toxicity grade is to be assigned as the AE toxicity grade when reporting on the AE eCRF. Vital sign abnormalities are not to be separately reported as AEs if the abnormality is part of a symptom complex that is already reported as an AE. 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 Reactogenicity

Reactogenicity (solicited systemic and injection site reactions) will be monitored by the site for 30 minutes after vaccination and thereafter assessed daily by the participants using e-diaries, starting on the evening after each vaccination, for at least seven days. 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, along with pre-paid return packaging to enable its return at the conclusion of all e-diary entries. Participants will also receive instructions on e-diary completion and be provided with an oral thermometer and injection site reaction

measurement tool on Day 1. Failure of a participant to comply with e-diary entry requirements will prompt compliance alerts being issued to the participant and to the clinical site, for site staff to follow up the noncompliance with the individual.

In the participant e-diary, information will be solicited on the following injection site reactions: warmth, tenderness, itching, pain, arm motion limitation, redness, induration, swelling, and bruising. In addition, information will be solicited on the following systemic reactions: tiredness, muscle ache, headache, and fever (oral temperature). The participant will be prompted to grade the severity of each reaction according to the instructions provided [eg, 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 treatment)]. 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 4). Use of such medications reported in the e-diary must be confirmed with the participant and recorded in the eCRF (refer to Section 6.5). Investigational site staff will review participant e-diary entries on a routinely basis (starting with the day following vaccinations) to assess compliance, need for re-instruction and evaluation against individual participant and study halting rules. On Days 15 and 29 (also the EWV if falling within a window for e-diary entry), the investigational site staff will review e-diary entries with the participant.

If 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 8.

For reactogenicity events with no direct corresponding symptom entry in Table 8 (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 8 will be translated to lay language in the e-diary instrument to promote participant understanding.

Participants will receive the measuring implements – oral thermometer and injection site reaction measurement tool – at the Day 1 visit, along with use instructions. Oral temperature (°F) will be recorded daily (at least once a day) by the participant in the e-diary. Using the injection site measurement tool, the participant will measure redness and/or swelling at the injection site and then grade these accordingly [ie, redness grade is based on greater of the two perpendicular measurements in centimeters, while swelling grade is based on greater of the two perpendicular measurements in centimeters and the functional scale (if applicable); see Table 8] in the e-diary. The PI may request the participant to attend an unscheduled study visit to evaluate any symptoms recorded in the e-diary.

8.4. Data Monitoring Committee(s)

8.4.1. 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 eCRF, potential AESIs of autoimmune etiology, or any other events the MM deems medically relevant) as determined by the MM on an ongoing basis, including any that result in study halt based on prespecified stopping rules (refer to Section 7.1). 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.

All DSMB reviews will be performed with blinded data, unless otherwise requested by the DSMB Chair. 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 interruption of dosing pending full DSMB evaluation.

A planned interim DSMB safety data review will be conducted after the first 500 participants have completed the Day 29 visit, comprising all safety evaluations through two weeks after the second vaccination. The DSMB will be supported by a (non-voting) unblinded statistician who will provide safety data (also demographics/baseline characteristics and protocol deviations) and otherwise assist in review activities as required.

The DSMB Chair will receive and evaluate each SAE, each severe AE (reported on the AE eCRF), and potential AESIs of autoimmune etiology. In addition, the MM may notify the DSMB Chair of any other medically relevant events (based on regular medical monitoring activities) for their review. The DSMB Chair will determine if an *ad hoc* review, in addition to the planned interim 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, on a blinded basis, all potential AESIs to assess cases for autoimmune etiology, if pre-existing or new onset, and relationship to the IP. Details on the recording of the AESI 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 clinical study participant administered a pharmaceutical 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, eg, 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 an other 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 Event of Special Interest

For this trial, an AESI is defined as any AE having an autoimmune etiology. Refer to Appendix B for a list of AESI terms defined by FDA's CBER that are potentially associated with autoimmune disease, and might represent a safety signal for vaccine-associated autoimmunity. Potential AESIs will be assessed by a member of the DSMB having expertise in this area (refer to Section 8.4.1). Once assessed as autoimmune in nature, the event will be considered as a confirmed AESI and recorded on the AE eCRF.

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 or from a clinical test result) will be recorded by the PI or designee on the AE eCRF if they

occurred from the time of the first vaccination on Day 1 up to Month 13, regardless of causal association with the IP. AE reporting is required for any new observation presenting after the first vaccination or for a deterioration of baseline condition (eg, increased severity/frequency). From the signing of the ICF until immediately before the first vaccination on Day 1, only AEs resulting from a study-related procedure will be recorded on the AE eCRF; all other events reported in this time period 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.

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

The severity of AEs will be assessed by the PI or designee using toxicity grading (Grade 1 to 4) according to a 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. For symptoms not appearing on the grading scale, the grading for generic "illness or clinical AE" will be used (refer to Table 8). For AEs being reported from clinical assessments, the PI or designee will refer to the specific sections on clinical laboratory tests (refer to Section 8.3.2), PEs (refer to Section 8.3.3), vital signs (refer to Section 8.3.4), and e-diary reactogenicity (refer to 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. The following guidelines are provided for this assessment.

- Unrelated: no relationship between the IP and the reported event
- Possibly related: the event follows a reasonable temporal sequence from the time of administration of investigational product and/or follows a known response pattern to the IP, but could also have been produced by other factors
- Probably related: a reasonable temporal sequence of the event with administration of IP exists and, based on the known response to the IP, known or previously reported adverse reactions to the IP or similar products, or in the PI or designee's clinical judgment the association of the event with the IP seems likely
- Definitely related: a definite causal relationship exists between the administration of the IP and the AE and other conditions (eg, concurrent illness, progression/expression of the disease state, 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.

9.3. Immediately Reportable Events

9.3.1. Principal Investigator's Reporting Requirements

The following events must be reported via email immediately (eg, within 24 hours of awareness) by the PI or designee to Emergent's Global Pharmacovigilance Department (Global PV):

- Any SAE regardless of causal association with the IP
- Any potential AESI, eg, AE of autoimmune etiology (refer to the list of AESI terms in Appendix B) regardless of causal association with the IP
- Any pregnancy where conception occurred after first exposure to the IP through Month 13

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

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 forms are not the same as the AE eCRF. Accompanying the form(s) will be source documentation or medical records (eg, discharge summary for hospitalizations, lab reports) which support a diagnosis. Participant identifiers (eg, 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 the IP through Month 13 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)).

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

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

9.4. Pregnancy

Women of childbearing potential must use an effective method of birth control from at least one month prior to Day 1 through Month 13. Methods of acceptable birth control are listed in Section 5.2.

Prior to trial enrollment, 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.

Pregnancy testing will be conducted at Screening and at specified time points during the study through Day 64/EWV (refer to Section 8.1). If a participant becomes pregnant between Screening and Day 1 prior to randomization, no IP is to be administered (refer to Section 8.1.2).

During the trial, all WOCBP will be instructed to contact the PI immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). Female participants must have a negative urine pregnancy test before receiving any vaccination. If the test is positive, vaccination will be suspended pending the outcome of a serum pregnancy test. Once pregnancy is confirmed, no further IP is to be administered to the participant. Participants will be encouraged to continue planned safety follow-up in the study. (Note, if the serum pregnancy test is negative, the vaccination visit may be rescheduled if it falls within the visit window for the visit, else the participant is to be discontinued from further vaccinations.)

If a participant becomes pregnant after the first vaccination, the investigational site staff will report the pregnancy to Emergent within 24 hours of awareness by completing the Pregnancy Notification Form and forwarding it to Global PV (refer to Section 9.3 for details). The Sponsor will forward a Pregnancy Outcome Form to the investigational site for monitoring the outcome of the pregnancy, including perinatal and neonatal outcomes. Separately, the PI or designee must also notify the IRB/IEC.

All pregnancies where conception occurred after first exposure to the IP through Month 13 are to be followed to outcome (eg, delivery, spontaneous/elective/therapeutic abortion), including after the study is completed and even if the participant is withdrawn from the study. When the PI or designee becomes aware of the outcome of the pregnancy, a Pregnancy Outcome Form will be completed and forwarded to the Global PV Department within 24 hours of awareness. While pregnancy itself is not considered an AE, pregnancy outcomes of spontaneous miscarriage, congenital anomaly, or birth defect are considered to be SAEs and must be reported according to the procedures described in Section 9.3. Elective abortions without complications will not be handled as AEs. As applicable, contact will be made when the infant is approximately 28 days old for a final follow-up, also reported on the Pregnancy Outcome Form.

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 subject 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 subjects 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 subjects 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 subjects 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 subjects or others is identified. Also, the investigator should notify Emergent and IQVIA of unanticipated problem(s).

9.6. Procedure for Breaking the Blind for Individual Subjects

In the case of a life-threatening emergency or pregnancy, the PI or designee may authorize unblinding of an affected participant in order to treat and ensure the safety of the participant. The PI will have 24-hour access to the IxRS for the purpose of unblinding and be trained in its use. IxRS access for unblinding will be set up for the PI to have sole access into IxRS for purposes of unblinding a participant and recording an unblinding event. Instructions to unblind treatment assignment within the IxRS system will be provided.

In the unlikely event that knowledge of the treatment assignment is necessary in order to treat or ensure the safety of a participant, PIs will make every effort to contact the study MMs (IQVIA MM and Emergent MM) prior to unblinding. This is not a mandatory requirement before unblinding, and in no way negates the PI's responsibility to make the final decision whether

unblinding is necessary. It is the PI's responsibility to inform the study MMs within 24 hours before unblinding to discuss the rationale for the unblinding; or if a study participant's treatment assignment is unblinded, the study MMs must be notified immediately, within 24 hours after the unblinding. The study MMs will immediately communicate instances of planned or unplanned unblinding with the Emergent Medical Officer (eg, within 24 hours of awareness of the situation).

In special circumstances, such as the occurrence of SUSARs or any safety signals, the study MMs in conjunction with the Emergent Medical Officer may also authorize unblinding for individual participants prior to database lock. It is not anticipated that all individual SAE reports will need to be unblinded. Additionally, the DSMB may recommend the unblinding of a particular participant (or participants) to the MM based on review of blinded data. The procedures for DSMB request to unblind participant(s) will be described in the DSMB Charter.

If a participant's study treatment assignment is unblinded for safety reasons, or if a participant becomes accidentally unblinded for any reason, the participant must (if applicable) be discontinued from receiving additional IP and will be requested to remain in the study for safety follow-up. Documentation of breaking the blind must be entered in the participant's source documents with the following information recorded: (1) date and time the blind was broken; (2) the rationale behind the unblinding decision/occurrence; (3) the names of the personnel involved; and (4) date/time of contact with the MM(s).

9.7. Follow-up of Adverse Events

All AEs/SAEs/AESIs will be followed until resolution, stabilization, or up to 30 days after the last study visit (Month 13).

9.7.1. Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified on the last scheduled visit (Day 64 or EWV) must be recorded on the AE eCRF with the current status noted. All nonserious events that are ongoing at this time will be recorded as "Not Recovered/Not Resolved" on the AE eCRF. The status of ongoing, previously reported AEs will be reviewed at the Day 64/EWV to determine if resolved. For participants that continue in the study beyond Day 64, the status of ongoing AEs will be queried at the quarterly phone contacts to determine and update the resolution status in the AE eCRF and any new nonserious AEs will be collected until last phone follow-up (Month 13).

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

This trial requires that participants be monitored for AEs/SAEs/AESIs up to Month 13. From Day 65 through Month 13, confirmed SAEs and confirmed (as assessed by the DSMB) AESIs will be recorded on the AE eCRF. The status of ongoing SAEs/AESIs after Day 64 will be reviewed at each quarterly safety phone contact to determine any new information and to update the resolution status in the AE eCRF.

The PI or designee will provide or arrange appropriate supportive care for participants for whom SAEs or potential AESIs are reported. Withdrawals of participants from vaccinations and/or the trial to treat SAEs/AESIs are at the discretion of the PI or designee, as subject to the guidance provided in Section 7.

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 the participant's condition even if the participant is seen by another physician, to obtain information about the diagnosis and 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:

- Subject withdraws consent
- Subject is referred to appropriate long-term medical care
- Subject is considered lost to follow-up (refer to Section 7.4 for description of contact attempts before a subject 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.

10. STATISTICAL ANALYSIS

The statistical analysis plan (SAP) will be finalized prior to the enrollment of the first participant and will provide additional details on the statistical methods described below.

10.1. Sample Size and Power Considerations

Sample size for this study is based primarily on safety considerations. The total sample size across all three AV7909 groups is set at 3300 participants. Allowing a 10% drop-out rate, this sample size for safety (3000) is sufficient to detect, with 95% probability, an AE rate of 1:1000, or 0.1%.

It is expected that more participants will be excluded from the immunogenicity analysis population (Per Protocol [PP] Population; refer to Section 10.2) than excluded from the Safety Population. A 25% exclusion rate from the PP Population is assumed. Thus, the PP Population will include approximately 800 participants for each AV7909 group (2400 participants total) and 400 participants for the BioThrax group.

Even under the best manufacturing practices, between-lot variation exists and will be considered normal. It is assumed that the lot-to-lot geometric mean titer (GMT) ratio could be as low as 0.6 based on Emergent's experience with the BioThrax vaccine. Conservatively, the largest GMT ratio between two out of three lots is assumed to be 1.5. Assuming a coefficient of variation of 100% (slightly larger than the observed 91% in the phase 2 study, EBS.AVA.208), this study has >99% power to demonstrate lot consistency with the pre-specified equivalence bounds ([0.5, 2.0]) in terms of GMT ratio for TNA NF_{50} at Day 64.

Based on the combined phase 1 and phase 2 data, the proportion of subjects receiving two doses of AV7909 on Day 1 and Day 15 with TNA NF_{50} at Day 64 over 0.56 is approximately 63% with lower 95% CI of 50% (total n = 54). Even assuming a conservative 50%, the study provides >99% power of rejecting the null hypothesis of 40% in each of the three AV7909 lots and in the combined AV7909 group (three lots pooled).

For the non-inferiority endpoint, among subjects (n = 184) receiving BioThrax PEP regimen (3 doses, SC) in the EBS.AVA.006 study, 93.5% had TNA NF_{50} values above 0.29 at Day 64. In the AV7909 phase 2 study (EBS.AVA.208), 86.5% of subjects (n = 37) had TNA NF_{50} above 0.29 at Day 64. Assuming a rate of 93% for the BioThrax group and 83% for the AV7909 group, the sample sizes of 400 and 2400 provide approximately 98% power to demonstrate non-inferiority of the two-dose AV7909 IM regimen to the three-dose BioThrax SC regimen at Day 64 with an non-inferiority margin of 15%.

10.2. Datasets for Analysis

The Intent-to-treat (ITT) Population will include all randomized participants.

The Safety Population will include all randomized participants who receive at least one vaccination. Safety analyses will be based on the Safety Population according to the vaccine received (BioThrax and combined AV7909 groups).

The PP Population used for analyses of immunogenicity will include participants who are randomized and do not have any of the deviations listed below:

- History of previous anthrax disease, anthrax exposure, or anthrax vaccination as per eligibility criteria, as evidenced by a baseline (Day 1 prevaccination) TNA NF_{50} above the limit of detection (LOD).
- Missing or out of window vaccination visit at Study Day 15
- Missing or out of window vaccination visit at Study Day 29 for the BioThrax group
- Administration issue(s) with IP, eg, incorrect dose of IP at one or more vaccination visits, administration of IP associated with a temperature excursion
- Use of prohibited or restricted medications which may have impacted immune response to vaccination as assessed by the Sponsor (this assessment will be completed prior to database lock)
- Missing immunogenicity data (eg, sample out-of-window, sample not shipped/received, sample not usable by the immunogenicity lab, sample associated with loss of cold chain) at Day 64

10.3. Handling of Missing Data

Unless otherwise specified, no imputation will be made for missing data.

Participants in the PP Population who have missing immunogenicity data at Day 29 will be excluded from Day 29 immunogenicity analysis, with the assumption that the missingness is completely at random since the participants will not have any knowledge about their immune response in terms of TNA NF_{50}.

TNA NF_{50} values below the lower limits of quantification (LLOQ) will be replaced by LLOQ/2 in the immunogenicity analyses.

10.4. Analysis of Disposition, Demographic and Baseline Characteristics

Disposition will be summarized for all participants who sign and date the ICF. Demographics and baseline characteristics will be summarized descriptively by group for both the ITT Population and PP Population. Medical history will be coded by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be tabulated by group (by ≥5% incidence) and also listed for the ITT Population.

10.5. Immunogenicity Analysis

Immunogenicity results by visit for each study group (AV7909 Lot 1, AV7909 Lot 2, AV7909 Lot 3, and BioThrax) and combined AV7909 group (three lots pooled) will include:

- Descriptive summaries (n, mean, SD, median, minimum, and maximum) of TNA NF_{50} values
- Geometric mean titer and corresponding 95% CIs for TNA NF_{50} values calculated by taking the anti-logarithms of the mean and 95% CIs for $\log_{10}$ TNA NF_{50}

- Proportion of participants with TNA NF_{50} ≥0.56 (also TNA NF_{50} ≥0.29 and TNA NF_{50} ≥0.15) with associated 95% CI (exact Clopper Pearson confidence limit).

Line plots of GMT with associated 95% CI for TNA NF_{50} by study group over time will be provided. Reverse cumulative distribution curve for TNA NF_{50} values on Day 29 and 64 will be provided.

10.5.1. Primary Immunogenicity Analysis

The primary immunogenicity endpoints will be tested in the hierarchy below. Testing of the next endpoint will only be carried out when all previous endpoints are met. According to the closed testing principle, this procedure ensures that the overall type I error rate is controlled at less than 5% and no additional adjustment is needed.

1a. AV7909 Lot Consistency Based on GMT Ratio of TNA NF_{50} at Day 64: the 95% CIs for the Day 64 TNA NF_{50} geometric mean ratios between all three pairs of AV7909 groups (Lot 1 vs. Lot 2, Lot 2 vs. Lot 3, and Lot 1 vs. Lot 3) are within 0.5 and 2.0.

1b. AV7909 Lot Consistency Based on Protective Level of Immunogenicity at Day 64: protective level of immunogenicity in all three consecutive AV7909 lots as demonstrated by the LB of the two-sided 95% CI to be ≥40% for the proportions of AV7909 participants in each of the three lots achieving a TNA NF_{50} ≥0.56 at Day 64.

The two endpoints 1a and 1b must both be met to demonstrate AV7909 lot consistency.

2a. AV7909 Immunogenicity at Day 64: once lot consistency is demonstrated, the immunogenicity data on Day 64 will be pooled across all three AV7909 lots. AV7909 will be considered as achieving a protective level of immunity under the US FDA's Animal Rule at Day 64 if the LB for the two-sided 95% CI for the proportion of participants with TNA NF_{50} values above the specified threshold of protection (≥0.56) is ≥40%.

2b. AV7909 Immunogenicity Based on Noninferiority vs BioThrax at Day 64: the difference in the proportion of participants with TNA NF_{50} values above the specified threshold of protection (≥0.29) will be calculated using the pooled AV7909 groups versus the BioThrax group. Noninferiority is demonstrated if the two-sided 95% lower CI of difference in proportions (AV7909 - BioThrax) is above -15%.

10.5.2. Secondary Immunogenicity Analysis

With respect to the secondary immunogenicity endpoint, AV7909 will be considered appropriately immunogenic under the US FDA's Animal Rule on Day 29 if the LB for the 95% CI for the proportion of participants pooled from all three AV7909 groups with TNA NF_{50} values above the specified threshold of protection (≥0.15) is ≥67%. The primary lot consistency and immunogenicity endpoints must all be met for testing to proceed to the secondary immunogenicity endpoint.

10.5.3. Exploratory Analyses

Predicted vaccine efficacy and 95% CI (based on pivotal animal study data) using the double-bootstrap method {Kohberger, 2007} and the observed TNA NF_{50} values (mean and standard

deviation [SD] of $\log_{10}$ TNA) will be calculated at Day 64 and Day 29 for the pooled AV7909 groups. The details of the calculation will be provided in the SAP.

10.6. Safety Analysis

10.6.1. Exposure

Exposure will be tabulated as the numbers and percentages of participants by group receiving each vaccination for all vaccinations administered and for vaccinations within the allowed visit windows and listed by individual participant according to the date and time and arm (left or right) of IP administration.

10.6.2. 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 summary categories of TEAEs (eg, any TEAEs, any drug-related TEAEs, any Grade 3 or 4 TEAEs) and using the MedDRA coded terms of SOC and PT overall, by ≥2% incidence in either group, and by severity (toxicity grade), seriousness, relationship to IP, and outcome (death, discontinuation of IP, study withdrawal) for each study group. A separate tabulation by MedDRA SOC and PT will be provided of treatment-emergent 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. An additional tabulation will be provided of TEAE incidences by MedDRA PT in decreasing frequency of the AV7909 (three lots pooled) group relative to the incidences in the BioThrax group. The incidences of AEs from the time of the first vaccination on Day 1 through Day 64, as well as incidences of AEs reported from Day 1 and up to Month 13 will be provided for AV7909 (three lots pooled) and BioThrax groups.

The proportions of participants with treatment-emergent SAEs and AESIs and associated two-sided 95% CIs will be provided for AV7909 (three lots pooled) and BioThrax groups. The relative risks for treatment-emergent SAEs and AESIs between AV7909 and BioThrax groups and associated 95% CIs will also be provided. No formal hypotheses testing will be conducted.

Separate listings will be prepared for AEs, deaths, SAEs, TEAEs leading to discontinuation of IP or study withdrawal, and AESIs.

10.6.3. 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 9 in Appendix A), and shifts from baseline will be summarized descriptively (number and percentage) by visit and group. Shift tables will be produced to reflect shifts from baseline

against the lab normal ranges (low, normal, high) as well as 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 (refer to Table 9 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 vaccination on Day 1 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 9 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.

10.6.4. 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.

10.6.5. Vital Signs

Vital signs data will be tabulated by visit and 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 vaccination on Day 1.

In listings, vital sign abnormalities associated with a severity grade based on the toxicity grading criteria (refer to Table 8 in Appendix A) will be flagged: Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, and Grade 4 = potentially life-threatening.

10.6.6. Prior and Concomitant Medications

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

10.6.7. Other Safety Variables

10.6.7.1. E-diary Reactogenicity

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 and group by severity grade. Participants reporting the same reaction multiple times will be counted once at the highest severity. Severity of fever will be attributed programmatically as follows:

- Grade 0: no fever (<100.4 ºF)

- Grade 1: 100.4–101.1ºF
- Grade 2: 101.2–102.0ºF
- Grade 3: 102.1–104.0ºF
- Grade 4: >104.0ºF

Summary statistics (n, mean, median, min, max, standard deviation) will additionally be provided for oral temperature and, for redness and swelling, the largest diameter of the affected area.

Listings and stacked bar charts with color coded severity will be provided for each symptom of systemic and injection site reactions.

E-diary compliance will be summarized by vaccination and group. Degree of compliance for a participant and vaccination will be calculated based on the expected total number of diary days, including extra days if there was an ongoing reaction, times the number of questions per day. The participant-level compliance percentage will be calculated for each vaccination, and then summarized using descriptive statistics.

10.6.7.2. Auto-antibody Testing

Results of auto-antibody testing will be listed by individual participant and tabulated.

10.7. Subgroup Analysis

To evaluate the consistency of immunogenicity and safety data across subgroups, TNA NF_{50} values on Day 64 and Day 29 and the incidences of TEAEs, SAEs, AESIs, and reactogenicity events will be summarized for AV7909 (three lots pooled) and BioThrax groups by age (18-30, 31-50 and 51-65), sex (male, female), and race (Caucasian, African American, other/more than one race). No formal statistical hypothesis testing will be performed.

10.8. Interim Analysis

No interim analysis on immunogenicity is planned for the study.

The DSMB will conduct a review of blinded safety data after the first 500 participants have completed he Day 29 visit, comprising all safety evaluations through two weeks after the second vaccination. All interim safety reviews, including possible *ad hoc* reviews requested by the DSMB Chair, will be performed with blinded safety data, unless otherwise requested by the DSMB Chair. Detailed scope of the safety review will be described in the DSMB Charter.

11. DATA HANDLING AND RECORD KEEPING

11.1. Source Documents and Access

Source documents are defined as the results 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, safety laboratory data/reports, memoranda, and recorded data from automated instruments (including e-diary). 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 defined 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 (DMP) documents. The standard operating procedures (SOPs) governing data management activities will be mutually agreed upon by the CRO and Emergent and documented in the DMP. Emergent will be 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 applicable). 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 site file is maintained in accordance with the ICH GCP 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. Records 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 to maintain 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 or its designee(s) 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 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 without prior written authorization from the Sponsor (refer to Section 14) and IRB/IEC, 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 five working days 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.

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 of 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. Blinded and unblinded CRO study monitors will be designated responsibilities according to the Monitoring Plan. Emergent personnel (blinded and unblinded) will perform oversight of the CRO monitoring function.

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)
- 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
- 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).
- Confirm that the e-diaries have been properly completed and reviewed by site personnel
- Record and report any protocol deviations not previously sent to Emergent
- Confirm AEs, AESIs, SAEs, and pregnancies have been properly documented (eCRF, SAE/AESI Report Form) and reported (sponsor, IRB/IEC)
- Confirm all pregnancies where conception occurred after first exposure to the IP through Month 13 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 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 will provide any needed assistance in responding to regulatory inspections.

13. ETHICS AND RESPONSIBILITY

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, current ICH 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 identification number will be used to identify each participant.

13.1. Informed Consent

The 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 GCP guideline, 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 (if applicable). 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 blinding 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 participating individuals. 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.

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 (eg, 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 will 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.

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 the primary outcome.

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

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

The toxicity grading scale 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 8 and Table 9, respectively (based on the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* {CBER, 2007}).

Table 8: 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

Toxicity	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potential Life-Threatening)
Hypotension – systolic (mmHg)	85–89	80–84	<80	ER visit or hospitalization for hypotensive shock
Respiratory rate (breaths/minute)	17–20	21–25	>25	Intubation
Systemic (General)				
Nausea/vomiting	No interference with activity or 1–2 episodes per 24 hours	Some interference with activity or >2 episodes per 24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2–3 loose stools or <400 g per 24 hours	4–5 stools or 400–800 g per 24 hours	≥ 6 watery stools or >800 g per 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; 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 Swelling is evaluated and graded using the functional scale as well as the actual measurement. Induration is graded using the functional scale.
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 minute. Clinical judgment will be used when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.
f Adverse event defined according to applicable regulations.

Table 9: Table for 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)	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
WBC increase (cell/mm^3)	10,800–15,000	15,001–20,000	20,001–25,000	>25,000

Panel and Analyte[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)[b]
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; PBRC = packed red blood cells; RBC = red blood cells; ULN = upper limit of normal range; WBC = white blood cell.
a Laboratory normal reference ranges have 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).

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 10: 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 (e.g., non-infectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis) • Cranial nerve disorders, including paralyses/paresis (e.g., 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
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.