Statistical Analysis Plan (SAP) for Study EBS.AVA.212: 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

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AV7909

STATISTICAL ANALYSIS PLAN

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
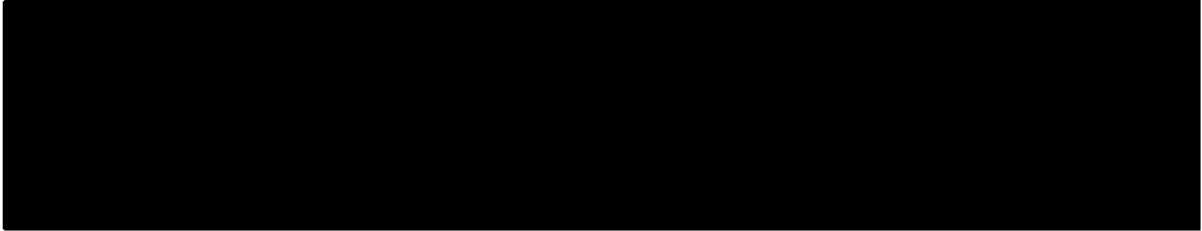
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Study Statistician
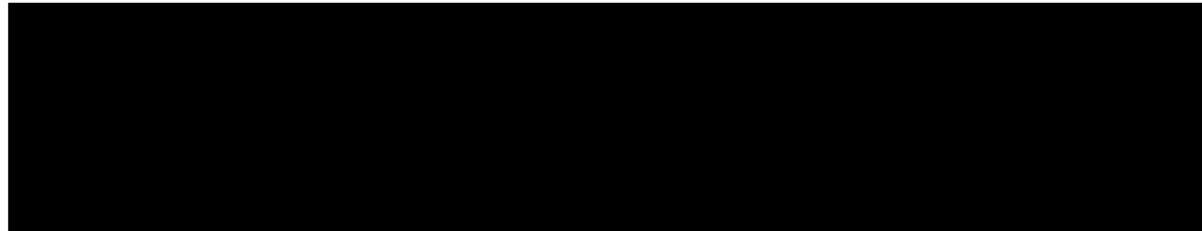

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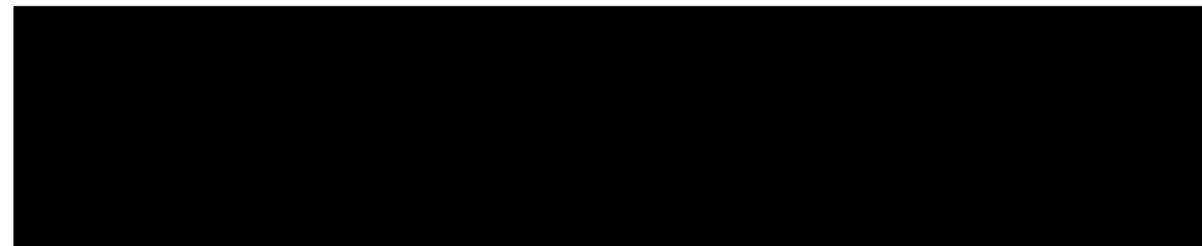
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Table 1   Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ANA	Anti-nuclear antibodies
ATC	Anatomical therapeutic chemical
AUC	Area under curve
AVA	Anthrax vaccine adsorbed
BARDA	Biomedical Advanced Research and Development Authority
cm	Centimeter
CBER	Center for Biologics Evaluation and Research
CI	Confidence interval
CRO	Contract research organization
CSR	Clinical study report
(ds)DNA	(double-stranded) Deoxyribonucleic acid
DSMB	Data safety monitoring board
eCRF	Electronic case report form
ED_{50}	50% effective dilution
e-diary	Electronic diary
ELISA	Enzyme-Linked Immunosorbent Assay
EWV	Early withdrawal visit
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GM(T)	Geometric mean (titer)
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
ID	Identification
IgG	Immunoglobulin G
IM	Intramuscular

IP	Investigational product
ITT	Intent to treat
IxRS	Interactive voice and/or web response system
kg	Kilogram
LB	Lower bound
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NF_{50}	50% neutralization factor
NHP	Nonhuman primate
PA	Protective antigen
PDMP	Protocol deviations management plan
PE	Physical examination
PEP	Postexposure prophylaxis
PI	Principal investigator
PP	Per protocol
PT	Preferred term (MedDRA)
PVE	Predicted vaccine efficacy
RF	Rheumatoid factor
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SDTM	Study data tabulation model
SOC	System organ class (MedDRA)
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TLF	Tables, listings, and figures
TNA	Toxin neutralizing antibody
TOST	Two one-sided test
TSH	Thyroid-stimulating hormone
US	United States

VE	Vaccine efficacy
WHO	World Health Organization
WOCBP	Women of childbearing potential

1   INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Protocol EBS.AVA.212 "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" (Version 4.2, 14 March 2019). This document specifies details of the definitions of the derived variables, analysis methods, assumptions and data handling conventions for the analyses of lot consistency, immunogenicity and safety to be included in the clinical study report (CSR).

2   PROTOCOL SUMMARY

2.1.   Study Objectives

2.1.1   Primary Objectives

- 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 non-inferiority 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.

2.1.2   Secondary Objectives

- 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

2.2   Study Design and Conduct

2.2.1   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 postexposure prophylaxis (PEP) of anthrax.

Healthy adults between 18 and 65 years of age (inclusive) will sign and date an informed consent form (ICF) 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 to one of four study groups on Day 1, as shown in Table 2. Randomization will be stratified by site. A representative racial distribution will be sought among recruited participants. Participants who are randomized and do not receive vaccination on the same day will be withdrawn from the study. The study schematic is provided in Figure 1.

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.
AV7909 = 0.5 mL AVA + 0.25 mg CPG 7909. Placebo=saline for injection. BioThrax = 0.5 mL AVA.

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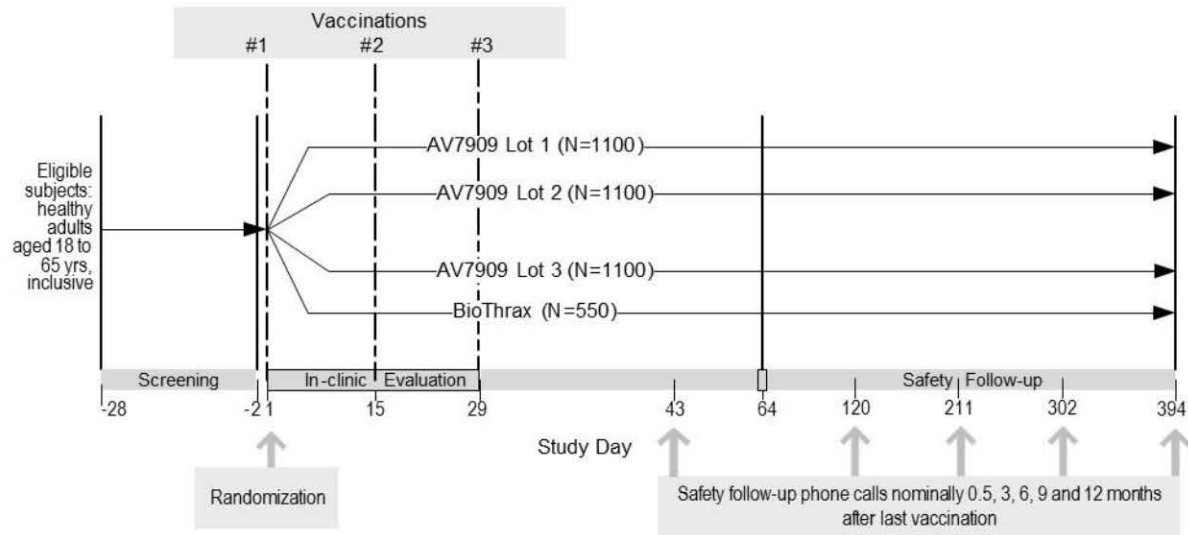
IM = intramuscular; SC = subcutaneous.
AV7909 is administered IM on Days 1 and 15, with placebo administered SC on Day 29.
BioThrax is administered SC on Days 1, 15, and 29.

2.2.2   Immunogenicity Testing

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 neutralizing antibody (TNA) assay. Blood samples will be collected at early withdrawal visit (EWV) only if it falls within the visit window for Day 64. 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}).

2.2.3 Safety Assessments

Participants will be evaluated for safety through Day 64 (or the 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). AESIs are AEs associated with autoimmune disease as defined by the Center for Biologics Evaluation and Research ([CBER]; refer to **Protocol EBS.AVA.212, Appendix B**), and might represent a safety signal for vaccine-associated autoimmunity. 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 pre-dose 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); i.e., 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.

2.2.3.1 Adverse Events

AEs (including SAEs and potential AESIs) will be recorded on the AE eCRF by the PI or designee if they occurred from the time of the first vaccination on Day 1 up to Month 13, regardless of causal association with the investigational product (IP). AE reporting is required for any new observation presenting after the first vaccination or for a deterioration of baseline condition (i.e., 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.

Refer to the specific sections in the Protocol EBS.AVA.212 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.

2.2.3.2   Clinical Laboratory Assessments

All analytes to be tested during screening/safety clinical laboratory tests are specified in **Protocol EBS.AVA.212, Table 7**.

The following assessments will be performed at Screening only:

- Urine drug screen (refer to Protocol EBS.AVA.212, 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 **Protocol EBS.AVA.212, 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 Protocol EBS.AVA.212, Section 5.1) are exempt from pregnancy testing. Vaccine will not be administered to any subject 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 as well as at the EWV if the EWV occurs before Day 29. Refer to Protocol EBS.AVA.212, 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).

All samples will be sent to the central laboratory for analysis, except urine for pregnancy testing in women of childbearing potential (WOCBP), which will be performed at the site and results documented in the eCRF.

2.2.3.3   Physical Examination

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

2.2.3.4   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, 5 and 29), vital signs will be assessed prior to vaccination and at 30 ± 5 minutes post vaccination.

2.2.3.5   E-Diary Reactogenicity

Reactogenicity (solicited systemic and injection site reactions) will be monitored by study site personnel 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. If injection site or systemic reactions continue beyond seven days, participants will be prompted to continue diary entries until they are symptom-free for two consecutive days.

In the 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 [e.g., 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)].

Oral temperature (°F) will be recorded daily (at least once a day) by the participant in the e-diary.

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; e.g., ibuprofen) or other medication in the past 24 hours. Use of such medications recorded in the e-diary must be confirmed with the participant and recorded in the eCRF.

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 [i.e., 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 **Protocol EBS.AVA.212, Section 9.1.2**]; result in discontinuation of study product or withdrawal from the study; or remain unresolved for 14 days or more.

2.2.3.6   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 Medical Monitor on an ongoing basis. The DSMB will comprise at least three voting members, to include one expert in immunology to specifically support the evaluation of potential AESIs for autoimmune etiology, if pre-existing or new onset, and relationship to the study product. All DSMB reviews will be performed with blinded data, unless otherwise requested by the DSMB Chair. The operations of the DSMB will be detailed in a DSMB Charter.

2.3 Study Endpoints

2.3.1 Primary Endpoints

The primary study endpoints are as follows:

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 $\geq$ 40% for the proportions of AV7909 subjects in each of the three lots achieving a TNA $NF_{50} \geq 0.56$ at Day 64.

Both of the two lot consistency endpoints should be met to demonstrate AV7909 lot consistency.

Immunogenicity:

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

2.3.2 Secondary Endpoints

The secondary study endpoints are as follows:

Immunogenicity:

- Lower bound of the two-sided 95% CI will be $\geq$ 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.

2.4   Sample Size and Power Considerations

Sample size for this study is based primarily on safety considerations. The total sample size across all three AV7909 study 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 3.2**) 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 participants 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 participants (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 participants (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%.

The sample size calculation was performed using PROC POWER in SAS/STAT 9.4.

2.5　Randomization and Blinding

2.5.1　Randomization

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 randomly assigned to one of the four study groups with the ratio of 2:2:2:1 (block size of 7) via an interactive voice and/or web response system (IxRS). 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. Randomized participants who withdraw from the study for any reason will not be replaced in this trial.

A randomization plan describing the method of treatment allocation and implementation of this method will be prepared and finalized prior to randomization of the first participant.

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. Participants who are screen failures are permitted to be rescreened one time (only) according to the PI's discretion. 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. Participants who complete the rescreening and are randomized in the study will not be considered screen failures.

2.5.2　Blinding

For this double-blind study, the site pharmacists or other designated, licensed study personnel who will prepare and/or administer the study vaccine/placebo will be unblinded to IP assignment. 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 representatives[s]), representatives of Biomedical Advanced Research and Development Authority (BARDA), contract research organization (CRO) staff (except unblinded statistician and unblinded study monitor[s] and unblinded Quality Assurance representative[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.

Under certain circumstances (e.g., safety reasons, required reporting to regulatory agencies), unblinding of IP for a particular participant is allowed. Otherwise, unblinding of the study will only occur after the clinical database has been locked. Refer to **Protocol EBS.AVA.212, Section 9.6** for procedures on how to break the blind for individual participants or procedures in case of accidental participant unblinding.

3 DATA CONSIDERATIONS

3.1 Protocol Deviations

A deviation occurs when site personnel or a participant does not adhere to the protocol's stipulated requirements, whether inadvertently or planned. All identified protocol deviations will be documented (entered in the CRO's Clinical Trial Management System or equivalent), classified, and reviewed on an ongoing basis through out the study according to procedures outlined in the Protocol Deviations Management Plan (PDMP). The final protocol deviation data will be reviewed and locked at the same time of database lock and incorporated into Study Data Tabulation Model (SDTM).

3.2 Analysis Populations

There will be three analysis populations for this study:

The Intent-to-treat (ITT) Population will include all participants who are randomized. Participants will be included in the study group to which they were randomized.

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 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 pre-vaccination) 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, e.g., 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 (e.g., 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

The PP Population will be used for analyses of lot consistency and immunogenicity. Participants will be included in the study group based on the vaccine received.

3.3 Analysis Time Points

Participant visits occur on protocol-specified days with associated visit windows. For purposes of data analysis, if the study day of assessment falls within the visit window, the corresponding analysis visit will be assigned as specified in Table 3 for vaccination, immunogenicity (TNA) testing, clinical laboratory data, vital signs, physical examinations, auto-antibiotic testing, and TSH assessment.

Table 3   Analysis Windows for Vaccination, Immunogenicity (TNA) Testing, Clinical Laboratory Data, Vital Signs, Physical Examinations, Auto-antibiotic Testing, and TSH Assessment

Analysis Visit	Nominal Day	Lower Limit	Upper Limit
Baseline	NA	-28	1, prior to the first vaccination
Day 1	1	1, since the first vaccination	1, since the first vaccination
Day 15	15	14	16
Day 29	29	27	31
Day 64	64	61	67

Out-of-window immunogenicity testing results will be excluded from the analyses for lot consistency and immunogenicity. Data at unscheduled visits might not be presented in the by-visit summary analyses, but will be included in the summary tables by maximum toxicity grade or abnormality and data listings. On vaccination days, vital signs will be taken before vaccination and at 30 minutes ($\pm$ 5 min) postvaccination, and therefore data will be tabulated for pre- and post-vaccinations, as appropriate.

3.4 Definition of Baseline

For all analyses, the baseline value is defined as the last non-missing value prior to the date and time of the first vaccination.

3.5 Selection of Data in the Event Multiple Records in an Analysis Window

For clinical laboratory data, vital signs, physical examinations, auto-antibiotic testing, and TSH assessment, if multiple valid non-missing observations exist in an analysis window for a specific visit, a single value will be chosen in the by-visit summary analyses based on the following rules:

- For baseline, the last available record prior to the date and time of the first vaccination will be selected.
- For post baseline visits,
    - if the analysis values are numeric and the toxicity grades are available, the record with the highest toxicity grade will be selected;
    - if the analysis values are numeric and the toxicity grades are identical or not available, the average (arithmetic mean) will be used;
    - if the analysis values are categorical, the most conservative value will be selected (e.g., abnormal will be selected over normal).

3.6 Treatment Groups for Analysis

Data analyses and summary tables by study group will be conducted and displayed as follows:

- The summary of immunogenicity response TNA NF_{50} will be presented for each of three lots of AV7909 study groups, AV7909 group (three lots pooled), and BioThrax group.

- For the AV7909 lot consistency analysis in terms of GMT ratio for TNA NF_{50}, data summary and analysis results will be presented for each of three lots of AV7909 study groups.

- For AV7909 immunogenicity on Days 64 and 29, data summary and analysis results will be tabulated for the combined AV7909 group (three lots pooled).

- For non-inferiority of AV7909 vs BioThrax on Day 64, data summary and analysis results will be tabulated with two groups: AV7909 (three lots pooled) and BioThrax group.

- All safety analyses (i.e., AEs), data summary and analysis results will be tabulated with two groups: AV7909 (three lots pooled) and BioThrax group.

Otherwise, data summary results will be displayed for each of three lots of AV7909 study groups, AV7909 group (three lots pooled), and BioThrax group. An overall 'Total' column will be included for participant disposition, demographics and baseline characteristics, protocol deviations, and exposure to study vaccinations.

3.7 Coding Dictionaries

Medical history and AEs will be coded to system organ class and preferred terms using the current version of Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 22.0.

Medications will be coded according to the latest version of the World Health Organization's (WHO) WHODrug Global Dictionary version prior to the database lock.

3.8 Toxicity and Severity Grading Scales

The toxicity grading scales (Grade 1 to 4) that will be used for safety assessment in this study are presented in **Protocol EBS.AVA.212, Appendix A** (Table 8 and Table 9), based on the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials* (**CBER, 2007**). The severity of AEs, vital signs, and reactogenicity events will be assessed by the PI or the designee. Clinical laboratory results will be graded by the central laboratory for analytes appearing in **Protocol EBS.AVA.212, Table 9**, reviewed by the PI or the designee. 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 **Protocol EBS.AVA.212, Table 8**). For reactogenicity assessment, a Grade of 0 will be available in the e-diary to record "symptom not present".

4   STATISTICAL ANALYSIS

4.1   General Considerations

All safety analyses will be performed based on the Safety population, and all the immunogenicity and lot consistency analyses will be based on the PP population.

Data summaries will be tabulated by treatment group as specified in Section **3.6**. Continuous variables will be summarized by descriptive statistics including number of non-missing observations (n), mean, standard deviation (SD), median, minimum and maximum; categorical variables will be summarized by the frequency count (n) and the percentage of participants (%) in each category.

All clinical laboratory data and vital sign data will be reported using standard international units, if applicable. The immunogenicity response TNA NF_{50} is a unitless quantitative result as it is derived from ED_{50} divided by the reference standard of ED_{50}.

The reporting conventions in **Appendix I** will be applied to all tables, listings, and figures, as appropriate.

All statistical analyses will be performed using SAS$^{®}$ v9.4 or later version.

4.2   Precision

Safety variables (i.e., clinical laboratory values, vital signs) including derivations thereof will be reported to the same precision as the source data. The immunogenicity response TNA NF_{50} will be reported with one decimal place or two significant digits (e.g., 0.032, 18.0).

4.3   Derived Variables

Study Day 1 is defined as the day of the first vaccination (same as the day of randomization). The day prior to Study Day 1 is Day -1. There is no Day 0.

In all data listings, study day relative to Study Day 1 will be presented. Study day relative to Study Day 1 will be calculated as:

- study day = (assessment date – date of first vaccination) if the assessment is before the date of first vaccination.
- study day = (assessment date – date of first vaccination + 1) if the assessment is on or after the date of first vaccination.

4.4   Handling of Missing Data

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

Immunogenicity response TNA NF_{50} values which are below the lower limit of quantification (LLOQ) will be handled according to the specifications in **Section 6**. 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}.

Descriptive safety presentations will be based on observed cases. To permit proper tabulation of AEs or medications, if appropriate, the following conventions will be used for imputation of completely and partially missing dates:

- For start date missing completely, impute the date of first vaccination

- For start date with missing day only, impute the 1st of the month unless month is same as month of first vaccination then impute the date of first vaccination.

- For start date with missing month and day, impute 1st January unless year is the same as the date of first vaccination then impute the date of first vaccination

- For end date missing completely, impute date of last contact

- For end date with missing day only, impute the last day of the month. If the month of the end date is same as month of last contact then impute the date of last contact

- For end date with missing month and day, impute 31st December or date of last contact, whichever is earlier

- If the end date is not missing and the start date is after the end date after missing value calculation, the end date will be used for the start date.

- An AE with completely missing both start and end dates, or with the start date missing and end date later than the date of first vaccination, will be considered to be treatment- emergent.

Missing start/end dates will appear as missing in the participant data listings.

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

4.5   Adjustment for Covariates

No formal model-based inferential analyses are planned using covariates and interactions.

4.6   Subgroup Analysis

To evaluate the consistency of immunogenicity results and safety profiles across subgroups, immunogenicity outcome (TNA NF_{50} on Day 29 and Day 64) and safety endpoints (incidences of TEAEs, SAEs, and e-diary reactogenicity) 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.

4.7   Multicenter Study

This study is expected to enroll 3850 participants at approximately 30-40 sites in the United States. Because of the large number of sites participating, test statistics adjusted for site are not planned. Subject enrollment and protocol deviations will be summarized by site.

4.8   Multiplicity Adjustment

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 lower bound (LB) of the two-sided 95% CI $\geq$ 40% for the proportion of AV7909 participants in each of the three lots achieving a TNA NF$_{50}$ $\geq$ 0.56 at Day 64.

Together, 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 NF50 values above the specified threshold of protection ($\geq$ 0.56) is $\geq$ 40%.

2b. **AV7909 Immunogenicity Based on Non-inferiority vs BioThrax at Day 64:** the difference in the proportion of participants with TNA NF50 values above the specified threshold of protection ($\geq$ 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 minus BioThrax) is above -15%.

Once all the primary endpoints (AV7909 lot consistency and immunogenicity) are satisfied, the secondary immunogenicity endpoint, AV7909 immunogenicity at Day 29, will be considered appropriately immunogenic under the US FDA's Animal Rule on Day 29 if the LB for the two-sided 95% CI for the proportion of participants pooled from all three AV7909 groups with TNA NF$_{50}$ values above the specified threshold of protection ($\geq$ 0.15) is $\geq$ 67%.

4.9   Data Issues Handling

4.9.1   Oral Temperature Data Errors

Oral temperatures are reported by participants in the e-diary for post vaccination reactogenicity. The numeric temperature values and the associated toxicity grades with temperatures less than 90 °F or greater than 110 °F will be set to null in the analysis.

4.9.2   Duplicate Enrollment at Different Sites

Eight subjects have been identified as being the same subjects that enrolled in 2 different sites, meaning only 4 unique subjects should be present in the study data and report. Data handling plans with respect to SDTM and data analysis are specified in **Appendix III** and **Appendix IV**.

5   STUDY POPULATION CHARACTERISTICS

5.1   Subject Disposition

Subject disposition will be summarized for all participants who sign and date the ICF. Tabulations will include the number of participants screened, randomized, vaccinated, completed study treatment (received all study vaccinations), discontinued study treatment, and withdrawn from the study prior to completion of the 12-month follow-up. Reasons for discontinuation of treatment and withdrawal from the study will be summarized.

The number and percentage of participants in each analysis population will be summarized by study group and overall for all randomized participants.

The number and percentage of participants enrolled by site will be provided by study group and overall based on the ITT population. Reasons for screen failure and reasons for exclusion from PP population will be summarized.

A listing of participants who discontinued IP or withdrawn from the study with reasons will be provided.

5.2   Protocol Deviations

Protocol deviations defined in **Section 3.1** will be summarized by site and deviation severity and category for each of the four study groups and overall for ITT Population.

A listing of protocol deviations will be provided.

5.3   Demographics and Baseline Characteristics

5.3.1   Subject Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized as continuous variables using descriptive statistics (n, mean, SD, median, minimum, and maximum) by study group (AV7909 Lot 1, AV7909 Lot 2, AV7909 Lot 3, AV7909 [three lots pooled], and BioThrax) and overall for ITT, Safety, and PP populations:

- Age (years)
- Baseline weight (kg)
- Baseline height (cm)
- Baseline BMI

The following demographics and baseline characteristics will be summarized as categorical variables with counts and percentages by study group and overall for ITT, Safety, and PP populations:

- Age (18 – 30, 31 – 50, and 51 – 65 years)
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, More than one Race, and Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)

Subject demographics and baseline characteristics data listings will be provided.

5.3.2 Medical History

Medical history that occurred in 1% or more participants in either AV7909 or BioThrax group will be tabulated by system organ class (SOC) and preferred term (PT), according to the Medical Dictionary for Regulatory Activities (MedDRA) for Safety population. A listing of medical history will be provided.

5.4 Treatment Compliance

The IP will be administered to the subject by the unblinded investigational site staff in a controlled, clinical environment with the date and time of vaccinations recorded (refer to the exposure analysis in **Section 7.1**).

6 IMMUNOGENICITY ANALYSIS

All the immunogenicity tabulations and figures will be based on the PP population as defined in **Section 3.2**. Immunogenicity outcome measures will be assessed by TNA NF_{50}. The validated LLOQ for TNA NF_{50} is 0.064 (**BBRC Study 762-G004690**). TNA NF_{50} values below the LLOQ will be imputed as 0.032 in the calculations of Mean/SD/GMT, which is half of the LLOQ of the assay. In the descriptive summary and data listing, TNA NF_{50} values which are below the LLOQ will be presented as "< LLOQ".

6.1 Summary of Immunogenicity Data

The summary of immunogenicity response TNA NF_{50} by visit for each of three lots of AV7909 study groups, AV7909 group (three lots pooled), and BioThrax group will include:

- Descriptive summaries (n, median, minimum, and maximum) of TNA NF_{50} values
- Geometric mean titer (GMT) and corresponding 95% CIs for TNA NF_{50} calculated by taking the anti-logarithms of the mean and 95% CIs for $\log_{10}$ TNA NF_{50}
- Proportion of participants with TNA $NF_{50} \geq 0.56$ (also TNA $NF_{50} \geq 0.29$ and TNA $NF_{50} \geq 0.15$) 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 Day 64 will be provided.

6.2 Primary Immunogenicity Endpoints

6.2.1 AV7909 Lot Consistency

6.2.1.1 Lot Consistency Based on GMT Ratio of TNA NF_{50} at Day 64

The AV7909 lot consistency analysis is performed by pair-wise comparison of the two-sided 95% CI on GMT ratio for TNA NF_{50} in each pair of lots (Lot 1 vs. Lot 2, Lot 2 vs. Lot 3, and Lot 1 vs. Lot 3) on Day 64. The lot consistency endpoint based on the GMT ratio for TNA NF_{50} will be met if all three 95% CIs fall within the equivalence range of [0.5, 2.0]. The linear regression model will be fitted with $\log_{10} NF_{50}$ (Day 64) as the dependent variable and lot as the independent variable (categorical), assuming common residual variance. The mean differences in $\log_{10} NF_{50}$ between all pairs of lots will be calculated with 95% CIs. These will be transformed (anti-log) back to the scale of GMT ratios.

6.2.1.2 Lot Consistency Based on Protective Level of Immunogenicity at Day 64

The protective level of immunogenicity in each of the three AV7909 lots at Day 64, under the US FDA's Animal Rule, is assessed by the proportion of participants with TNA NF_{50} values ≥ 0.56 on Day 64. The proportion and two-sided 95% CI (exact Clopper-Pearson confidence limits) for the proportion will be provided for each of the three AV7909 lots. This lot consistency based on the protective level of immunogenicity will be met if the LB of the two-sided 95% CI of the proportion is $\geq 40\%$ for all three AV7909 lots.

6.2.2 AV7909 Immunogenicity

6.2.2.1 AV7909 Immunogenicity at Day 64

The immunogenicity of AV7909 on Day 64 will be assessed by the proportion of participants pooled across all three AV7909 lots with TNA NF_{50} values ≥ 0.56 on Day 64. The proportion and two-sided 95% CI (exact Clopper-Pearson confidence limits) for the proportion will be provided for the combined AV7909 group (three lots pooled). AV7909 will be considered as achieving a protective level of immunogenicity at Day 64 if the LB of the two-sided 95% CI of the proportion is $\geq 40\%$.

6.2.2.2 AV7909 Immunogenicity Based on Non-inferiority vs BioThrax at Day 64

Non-inferiority of AV7909 versus BioThrax on Day 64 is satisfied if the LB for the two-sided 95% lower CI of the difference (AV7909 - BioThrax) in the proportion of participants with TNA NF_{50} values ≥ 0.29 in the combined AV7909 group (three lots pooled) versus BioThrax group is $> -15\%$.

The within-group proportions and the associated two-sided 95% CIs (exact Clopper-Pearson confidence limits) will be provided for the combined AV7909 group (three lots pooled) and

BioThrax group. The treatment difference in proportion between the combined AV7909 group and BioThrax group and two-sided 95% lower CI will be calculated using Newcombe score method.

6.3   Secondary Immunogenicity Endpoint

The immunogenicity of AV7909 on Day 29 will be assessed by the proportion of participants in the combined AV7909 group (three lots pooled) with TNA NF_{50} values ≥ 0.15 on Day 29. The proportion and two-sided 95% CI (exact Clopper-Pearson confidence limits) for the proportion will be provided for the combined AV7909 group (three lots pooled), and the LB of the CI is compared with the success criterion of 67%. AV7909 will be considered as achieving a protective level of immunogenicity under the US FDA's Animal Rule at Day 29 if the LB of the two-sided 95% CI of the proportion is $\geq 67\%$.

6.4   Exploratory Immunogenicity Endpoints

Predicted vaccine efficacy (PVE) and associated 95% CI will be calculated at Day 64 and Day 29 for the combined AV7909 groups using efficacy data from Emergent's nonhuman primates GLP **Study 3655-100072763** and the observed TNA values in this clinical study. The computational algorithm with double-bootstrap method to calculate confidence intervals proposed by Kohberger (**Kohberger, 2007**) will be used. The details are provided in **Appendix II**.

6.5   Subgroup Analyses for Immunogenicity

Subgroup analyses of immunogenicity data will be tabulated by age group, sex, and race as described in **Section 4.6** in the similar manner as specified in **Section 6.1**. Line plots of estimated GMT with associated 95% CI for TNA NF_{50} over time by subgroup variable and treatment group will be provided.

7   SAFETY ANALYSIS

All safety data will be presented based on the Safety Population. Data summaries will be tabulated by two treatment groups, AV7909 (three lots pooled) and BioThrax group. Continuous variables will be summarized using number of participants (n), mean, SD, median, minimum, and maximum; categorical variables will be summarized by the number (frequency) and percentage in each category.

7.1   Exposure to Study Drugs

Exposure will be tabulated as the numbers and percentages of participants by vaccination and treatment group (AV7909 and BioThrax) for all vaccinations administered and for per-protocol vaccinations. Per-protocol vaccinations include vaccinations administered without any administration issues, eg, incorrect product administered, incorrect dose of IP, incorrect route, missing previous dose, and outside the acceptable visit windows on Days 1 (NA), 15($\pm$1) and 29($\pm$2). The data listing including date and time of IP administration and injection location (left or right arm) will be provided.

7.2 Adverse Events

All adverse events will be coded to system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

7.2.1 Overall Summary of TEAEs

A treatment-emergent adverse event (TEAE) is defined as an AE that presents after the initiation of treatment or any AEs already present that worsen in either intensity or frequency following treatment. For programming purpose, any AEs with start date on or after the start date of the first vaccination will be counted as treatment-emergent. AEs with missing start dates, but with end dates later than the date of first vaccination will also be counted as treatment emergent.

An overall summary table with the following TEAE categories will be provided:

- TEAEs
- Vaccine-related TEAEs
- Grade 3 or 4 TEAEs
- Vaccine-related Grade 3 or higher TEAEs
- Serious TEAEs
- Serious vaccine-related TEAEs
- Death
- TEAEs leading to discontinuation of vaccination
- TEAEs leading to study withdrawal
- AESIs
- Vaccine-related AESIs

7.2.2 All TEAEs

All TEAEs will be summarized by SOC and PT in descending order of participant incidence in AV7909 group (three lots pooled).

TEAEs that occurred in 1% or more for a PT term in either AV7909 group or BioThrax group will be tabulated by SOC and PT.

All TEAEs will be summarized by severity to IP, SOC, and PT for AV7909 (three lots pooled) and BioThrax group. All TEAEs will be summarized by relationship to IP, SOC, and PT for AV7909 (three lots pooled) and BioThrax group. Participants having the same TEAE more than once will be counted once for each PT and once within each SOC at the maximum severity and relatedness. If the severity/relatedness is missing for one or more of the occurrences, the maximum severity/relatedness of the remaining occurrences will be used.

For the analysis purpose of one of the secondary safety endpoints, the incidences of AEs from the time of the first vaccination on Day 1 through Day 64, where so indicated, selected

AE summaries will be provided for all TEAEs and for TEAEs reported during study period Day 1 to Day 64, respectively.

A participant data listing of all AEs (including treatment-emergent AEs (TEAEs) and non-TEAEs) sorted by site, study group, subject ID and AE start date/time will be provided. This listing will include a "Treatment-emergent" flag. Separate listing will be provided for Grade 3 or 4 TEAEs.

7.2.3   Serious TEAEs

Serious TEAEs will be summarized by SOC and PT. Serious TEAEs will be summarized by relationship to IP, SOC, and PT for AV7909 (three lots pooled) and BioThrax group as well.

A participant data listing of all serious AEs (both TEAEs and non-TEAEs) will be provided.

The safety outcome measure used for the primary safety analysis is the incidence rate of serious TEAEs. The within-group proportion of participants with serious TEAEs and associated two-sided 95% CI (exact Clopper-Pearson confidence limits) will be provided for AV7909 (three lots pooled) and BioThrax group. The relative risk (ratio of proportion of participants with serious TEAEs in AV7909 vs. BioThrax group) with exact unconditional 95% CI will be provided for treatment comparison between the two groups. No formal hypothesis testing will be conducted.

7.2.4   Adverse Events of Special Interest (AESI)

Treatment-emergent AESIs determined to be of autoimmune etiology based on decision of the DSMB will be summarized by SOC and PT, listed by individual participant.

The incidence rate of treatment emergent AESIs will be summarized and analysed in the similar manner as described in **Section 7.2.3**.

7.2.5   TEAEs Leading to Discontinuation of Vaccination and Leading to Study Withdrawal

Separate tables and listings will be prepared for TEAEs leading to discontinuation of the vaccination, and TEAEs leading to withdrawal from the study.

7.2.6   Deaths

A large number of deaths is not expected in this study with healthy participants. A tabulation and participant data listing of all deaths will be provided.

7.3   Clinical Laboratory Tests

Clinical laboratory results for the lab analytes that appear in **Protocol EBS.AVA.212, Table 9** will be assigned by the central laboratory a toxicity grade (Grade 1=mild through Grade 4=potentially life-threatening).

Central laboratory measurements will be tabulated by treatment group (combined AV7909 and BioThrax) as follows:

- Observed values and changes from baseline of continuous laboratory variables (hematology, serum chemistry, and selected urinalysis parameters [e.g., specific gravity]) will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum) by study visit and treatment group.

- Observed values of categorical laboratory analytes (e.g., urinary protein) and shifts from baseline (number and percentage) will be summarized by study visit and treatment group.

- Shift from baseline according to normal reference ranges (reported as 'Low', 'Normal', and 'High') will be summarized (number and percentage) by study visit and treatment group.

- Shift from baseline according to toxicity grading criteria grade (Grade 0, Grade 1-4) will be summarized (number and percentages) by study visit for analytes that appear in **Protocol EBS.AVA.212, Table 9**. Grade 0 includes all values within normal range or value not meeting criteria for toxicity of at least Grade 1.

- Frequency and percentage of participants with the highest grade of post baseline abnormal laboratory values according to toxicity grading criteria grade (Grade 1-4).

Laboratory data listing will be provided with all test results that are collected throughout the study per analyte for participants who have at least one abnormal result based on the reference range or with Grade 1 to Grade 4 based on toxicity grading criteria at any time of study. All applicable severity grades or abnormal flags displayed. A separate data listing will be provided with Grade 3 or above laboratory observations.

7.4   Vital Signs

Vital sign data will be assigned a toxicity grade (Grade 1=mild through Grade 4=potentially life-threatening) according to **Protocol EBS.AVA.212, Table 8**. For heartbeat and blood pressure, there are toxicity criteria for both increased and decreased levels; analyses for each direction (i.e., increased, decreased) will be presented separately.

Vital signs data will be summarized as follows:

- Observed values and changes from baseline by study visit and treatment group (AV7909 and BioThrax).

- Shift from baseline according to toxicity grading criteria grade (Grade 0, Grade 1-4) (number and percentages) by study visit and treatment group. Grade 0 includes all values not meeting criteria for toxicity of at least Grade 1.

All vital sign records will be provided in the participant data listings. This listing will include all results that are collected throughout the study for the analyte of interest, with all applicable severity grades displayed. A separate data listing will be provided with Grade 3 or above vital sign observations.

7.5   Physical Examinations

Complete and symptom-directed PE findings will be tabulated including number of participants with normal/abnormal PE findings by body system and study visit for each of the two treatment groups (AV7909 and BioThrax). Listings will be provided with all abnormal findings.

7.6   Prior and Concomitant Medications

Prior and concomitant medication information will be coded according to the World Health Organization's (WHO) WHODrug Global Dictionary. Data will be tabulated by Anatomical Therapeutic Chemical (ATC) classification level 4, medication preferred term, and treatment group (AV7909 and BioThrax) for prior and concomitant medications. A participant data listing of all medications will be provided.

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. For purposes of analysis, any medication with an end date between 30 days or less before date of screening and on or prior to the first vaccination, the date will be categorized as prior. Any medication which is ongoing or with an end date that is after the first vaccination date will be categorized as a concomitant medication. Partial dates will be imputed according to **Section 4.4**. The summary will be sorted in descending order of percentage in the AV7909 group by drug class and drug name within a class. For drugs with the same frequency, sorting will be done alphabetically.

7.7   Other Safety Analyses

7.7.1   E-diary Reactogenicity

E-diary reactogenicity data will be summarized with number and percentage of participants with the highest severity grade for each symptom of solicited systemic reactions (tiredness, muscle ache, headache, and fever) and injection site reactions (warmth, tenderness, itching, pain, arm motion limitation, redness, induration, swelling, and bruising) by severity grade and treatment group post each vaccination. Severity of fever will be attributed programmatically using oral temperature measurement reported in the e-diary according to grading scale for fever in **Protocol EBS.AVA.212, Table 8**.

Stacked bar charts with color coded severity and participant listings will be provided for each symptom of systemic and injection site reactions.

7.7.2   In-clinic Reactogenicity

In-clinical reactogenicity data will be summarized in the similar manner as those for e-diary reactogenicity, except for fever (oral temperature) which will be reported and presented as vital sign observations at 30 minutes post vaccinations.

All in-clinical reactogenicity data will be provided in the data listings.

7.7.3   E-diary Compliance

E-diary compliance will be summarized by vaccination and treatment group (AV7909 and BioThrax). 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.

7.7.4   Auto-antibody Testing and TSH Assessment

Auto-antibody testing of RF, ANA and anti-dsDNA antibodies and TSH assessment will be tabulated with negative/positive results by study visit and treatment group (AV7909 and BioThrax) and subject listing will be provided with all test results that are collected throughout the study per analyte for participants who have at least one abnormal result at any time of study.

7.7.5   Pregnancy

Participant listing with all FSH test results will be provided. Pregnancy data listing (serum and urine) will be provided with all test results that are collected throughout the study for participants who have at least one positive result.

7.8   Subgroup Safety Analyses

The incidences of TEAEs and SAEs will be tabulated by SOC, PT, and by subgroup variables age, sex, and race as defined in **Section 4.6**. Solicited systemic and injection site reactions will be tabulated by these subgroup variables in the similar manner as described in **Section 7.7.1**.

8   INTERIM ANALYSES

No interim analysis on immunogenicity is planned for the study.

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. 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.

9   CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

No changes impacting the conduct of the study or planned primary and secondary analyses have been made..

10 REFERENCES

1. CBER, Center for Biologics Evaluation and Research [Internet]. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. September 2007. Accessed 19 Jun 2018: https://www.fda.gov/downloads/BiologicsBloodVaccines/ucm091977.

2. BBRC Study 762-G004690, "Two Site Validation of the Human High Throughput Toxin Neutralization Assay (htpTNA) Conducted in Conjunction with Validation Protocol VP2007-164".

3. Study 3655-100072763, "GLP Study Evaluating the Efficacy and Toxin Neutralizing Antibody (TNA) Threshold of Protection. in Nonhuman Primates Immunized with AV7909 14 Days Apart and Challenged with Bacillus anthracis on Days 28 or 70 Post-First Immunization".

4. Kohberger R. Correlates of protection: methods and validation. Anthrax vaccines: bridging correlates of protection in animals to immunogenicity in humans; 2007 Nov 8-9; Gaithersburg, MD.

5. Emergent global standard operating procedure, Production and Control of Statistical Analysis Plan (SAP) and SAP Amendments. SOP003107, version 3.0, effective on 02 Feb 2017.

6. Emergent global standard operating procedure, Statistical Oversight of Clinical Studies. SOP041684, version 2.0, effective on 18 Sep 2018.

7. Emergent global standard operating procedure, Database Lock. SOP002988, version 3.0, effective on 12 Jun 2017.

8. Emergent global standard operating procedure, Production of Tables, Listings and Figures for Clinical Study Reports and Regulatory Submissions. SOP041908, version 0.3, Ready for Approval.

9. IQVIA Operating Procedure, Statistical Principles. CS_OP_BS001 Revision 11, effective on 15 Mar 2018.

10. IQVIA Operating Procedure, Ensuring Quality in Biostatistical Deliverables. CS_OP_BS0216 Revision 2, effective on 1 Aug 2016.

APPENDICES

APPENDIX I   TABLE/LISTING/FIGURE TEMPLATE GUIDANCE

1.   Convention for All Outputs

- Unless otherwise specified, all computer-generated table/listing/figure (TLF) outputs should be produced in landscape mode. Required margins: 1 inches on top and bottom and 1 inch on the left and right; required font: Courier New; and required font size: 8, at the minimal.

- Single line space is the standard for all TLFs.

- All output should have the following header at the top of the page:

  Emergent BioSolutions Inc. < left adjusted>   Page x of y < right adjusted>

  Protocol EBS.AVA.212 < left adjusted>

  TLFs should be internally paginated in relation to total length (i.e., page number should appear sequentially as page x of y, where y is the total number of pages in each table, listing, or figure).

- Each output should be identified by a numeral, and the output designation (e.g., Table 1) should be listed on the same line, before the title. A decimal system (x.y and x.y.z) should be used to identify tables and listings with related contents. The title is centered and spelled out in title case.

  <center>Table <Table No> Table Title
Study Population</center>
  The study population should be identified immediately following the title. Insert a blank line after the last title and before the body of the TLF content.

- Footnotes should be single spaced, but separated by at least a double space from the bottom line of the table. The notes are aligned vertically by the left vertical border of the table. Footnote should be ordered as follows, if appropriate:

  - Footnote 1: source listing and/or Dictionary version, if needed.

  - Footnote 2: treatment group(s), if needed.

  - Footnote 3: abbreviation footnotes (if needed; all abbreviations must be defined): Separated by semi-colon, ended by period. One space before/after "=". Display in alphabetical order.

  - Add other notes if needed.

  - Last footnote: program path, program run date, data cut-off date. Insert a blank line before the last footnote.

- Column headings should be in title characters. For numeric variables, include "unit" in column or row headings when appropriate.

- For the text within the table body and not directly from the data, only capitalize the first letter of the first word as in a sentence, and do not capitalize the first letter of each word (i.e., sentence case).

2. Table Convention

- Unless otherwise specified in the TLF shell, decimal places for numeric results:

    - If not otherwise specified, mean, geometric mean, standard deviation, median, minimum, maximum, and CI values will be formatted with the same number of decimals found in the raw data.

    - One decimal point or two significant digits (e.g., min 0.032 max 18.0) is presented for TNA NF_{50}.

    -

    - Geometric mean ratio will be formatted with two decimal places.

- P-values will be 2-sided and presented with 2 significant digits, i.e. 0.45, 0.045. P-values less than 0.001 will be presented as "< 0.001".

- Unless otherwise specified, CIs are two-sided with 95% confidence.

- For numerical variable data summary, align decimal point of each statistics across rows. For 95 CI, align the ',' with the decimal point of above statistics.

```
                       Group 1         Group 2         Group 3
                       (N=xxx)         (N=xxx)         (N=xxx)

Parameter 1
   n                   xx              xx              xx
   Mean                xx.x            xx.x            xx.x
   SD                  xx.xx           xx.xx           xx.xx
   Median              xx.x            xx.x            xx.x
   Min, Max            xx, xx          xx, x           xx, xx
```

- For categorical variables, the number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses. Percentages will be calculated using a denominator of all participants in a specified analysis population (and present at the analyzed visit in by-visit summaries). The denominator will be specified in a footnote to the tables for clarification where necessary. All percentages will be rounded to one decimal place. Unless otherwise specified, the "N=xx" under each column header will represent the number of participants in that group, and all percentages below will be based on this number. Align count (integer) and first parenthesis across each row. Align decimal place of percentages and zero frequencies (present as 0, no percentage).

- Each level of indentation within a table takes a space of 2 characters.

	Group 1 (N=xxx) n (%)	Group 2 (N=xxx) n (%)	Group 3 (N=xxx) n (%)
	xx (100.0)	xx (100.0)	xx (100.0)
	0	xx (xx.x)	x (x.x)
	xx (xx.x)	0	xx (xx.x)
	xx (x.x)	x (x.x)	xx (xx.x)
	x (x.x)	x (x.x)	0

3. Listing

Convention

- Listings should be sorted by site, study group, subject numbers and (if applicable) visit day/time or sequence number. Values from repeat tests and unscheduled visits should be presented chronologically with values from scheduled visits.

- In a listing, the subject number should be displayed only once for the subject with multiple records. If a subject's records run into multiple pages, display the subject number once for every page.

- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote (" - = unknown or not evaluated"), or as "N/A," with the footnote "N/A = not applicable," whichever is appropriate.

- Dates should be printed in SAS® DATE9.format ("DDMMMYYYY": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- Time should be printed in SAS® TIME5.format ("HH:MM": 17:30). Missing portions of time should be represented on subject listings as dashes (--:30). Times that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

4. Graphic Convention

- Each container document will be in MS Word format.

- Graphic object output will be in *WMF, TIFF, or JPEG* format.

- Same plot produced for each treatment group will have same axis ranges.

- Define line and symbol types as below:

Table 4   Line and Symbol Types in Graph

Attribute	Parameter	Value/Line
Line	< Treatment group 1 >	Line Type = 1
	< Treatment group 2 >	Line Type = 2
	< Treatment group 3 >	Line Type = 3
	< Treatment group 4>	Line Type = 4
Symbol	< Treatment group 1 >	Symbol = circle
	< Treatment group 2 >	Symbol = triangle
	< Treatment group 3 >	Symbol = square
	< Treatment group 4 >	Symbol = empty circle

APPENDIX II CALCULATION OF PREDICTIVE VACCINE EFFICACY USING KOHBERGER METHODOLOGY

1. Methodology for Calculation of Predictive Vaccine Efficacy

To calculate predictive vaccine efficacy (VE), a method previously described by Dr. Robert Kohberger in the Anthrax Vaccines: Bridging Correlates of Protection in Animals to Immunogenicity in Humans, Workshop Proceedings, 2007 is used. The calculation uses both animal and human data.

VE (%) is defined as:

$$VE = (1 - (1 - p_v)/(1 - p_u)) \times 100\%$$

where p_v is the population probability of survival in vaccinated individuals and p_u is the probability of survival for the unvaccinated. In our calculation, it is assumed that $p_u = 0$. Since p_v cannot be estimated directly, it is predicted by utilizing the data from animal challenge study with serum TNA NF_{50} values as bridging correlate of protection.

To calculate predicted VE:

1. Fit a logistic regression mode to the animal (NHP) survival data ($Y = 1$ if survived) with TNA NF_{50} values (log transformed) on the day before challenge as predictor X.

$$\text{logit}(\Pr(Y = 1)) = \alpha + \beta X$$

2. Using the parameter estimates from logistic regression model in step 1 and human TNA NF_{50} results to estimate the probability of survival for subject i:

$$\hat{p}_{v,i} = \frac{1}{1 + \exp(-\hat{\alpha} - \hat{\beta} x_i)}$$

   where x_i is a log-transformed TNA NF_{50} value for subject i at Day 64 (or Day 29 for early protection).

3. The average probability of survival for all study subjects is $\hat{p}_v = \text{sum}(\hat{p}_{v,i}) / n$, where n is the number of subjects in the immunogenicity analysis population.

4. Predicted VE $= \hat{p}_v \times 100\%$.

To derive a confidence interval for the predicted VE, we use a double-bootstrap method with the following steps:

1. Resample the animal data (TNF NF_{50} on the day before challenge, and survival status) with replacement.

2. Resample the human TNF NF_{50} data with replacement.

3. For each pair of animal-human bootstrap datasets generated above, repeat the steps described above to calculated predicted VE.

4. Repeat the double-bootstrap steps 1-3 for N times.

5. Rank the resulted N bootstrap predicted VE values from smallest to largest. The 2.5% and 97.5% percentiles are taken to be the 95% confidence interval for the predicted VE.

2.   Description of Animal Data

The animal data used in Step 1 above were collected from Emergent nonhuman primates GLP Study 3655-100072763. One hundred sixty-four (164, 82 male and 82 female) Asian-origin cynomolgus macaques (Macaca facicularis) were randomized to one of 16 groups with equal numbers of males and females per group as shown in Table 5. Animals were vaccinated with AV7909, BioThrax, or saline intramuscularly on Study Days 0 and 14. Animals were aerosol challenged on Study Day 28 or 70 (depending on group assignment) with a targeted dose of Bacillus anthracis (Ames strain) spores that exceeded the median lethal dose (LD_{50}) by 200-fold (200 LD_{50}).

Table 5   Study Design of Study 3655-100072763

Group	Number of Animals	Vaccine	Dilution	Immunization Days	Challenge Day	End-in-life Day
1	8	AV7909	1:4	0, 14	28	58
2	8	AV7909	1:16	0, 14	28	58
3	16	AV7909	1:32	0, 14	28	58
4	16	AV7909	1:64	0, 14	28	58
5	8	AV7909	1:128	0, 14	28	58
6	8	AV7909	1:192	0, 14	28	58
7	8	BioThrax	1:64	0, 14	28	58
8	10	Saline	N/A	0, 14	28	58
9	8	AV7909	1:4	0, 14	70	100
10	8	AV7909	1:16	0, 14	70	100
11	16	AV7909	1:32	0, 14	70	100
12	16	AV7909	1:64	0, 14	70	100
13	8	AV7909	1:128	0, 14	70	100
14	8	AV7909	1:192	0, 14	70	100
15	8	BioThrax	1:64	0, 14	70	100
16	10	Saline	N/A	0, 14	70	100

Following challenge, animals were observed twice daily for survival through Study Day 58 or 100 (depending on group assignment). Blood collections for TNA (NF_{50} and ED_{50}) and anti-PA IgG ELISA were performed on Study Days 0 (prior to vaccination), 14 (prior to vaccination), 28 (prior to challenge), and 58 for Groups 1 through 8 and Study Days 0 (prior to vaccination), 14 (prior to vaccination), 28, 35, 42, 70 (prior to challenge), and 100 for Groups 9 through 16.

To calculate the predicted VE at Day 29, AV7909-vaccinated animals (Groups 1 through 6) are included in the logistic regression model with the animal survival outcome ($Y = 1$ if survived) as response and TNA NF_{50} values (log 10 transformed) on Study Day 28, before

challenge on the same day, as predictor. Figure 2 displays the fitted logistic regression curve along with 95 percent confidence intervals for Study Day 28. To calculate the predicted VE at Day 64, AV7909-vaccinated animals (Groups 9 through 14) are included in the logistic regression model with animal survival outcome as response and TNA NF_{50} values (log 10 transformed) on Study Day 70, before challenge on the same day, as predictor. Figure 3 displays the fitted logistic regression curve along with 95 percent confidence intervals for Study Day 70. In Figure 2 and 3, it shows that one death event (Figure 2) and two death events (Figure 3) occurred to animals with TNA NF_{50} above the LLOQ. In the bootstrap resampling data, Firth correction will be used to handle the quasi separation.

The LLOQ for TNA NF_{50} for NHP is 0.105. Titers less than the LLOQ were replaced with the LLOQ for the statistical analysis.

Figure 2   Study 3655−100072763 Fitted Logistic Regression Model for Survival in the AV7909 Vaccinated Groups (1−6) as a Function of Log_{10} TNA NF_{50} on Study Day 28−Challenge Day 28
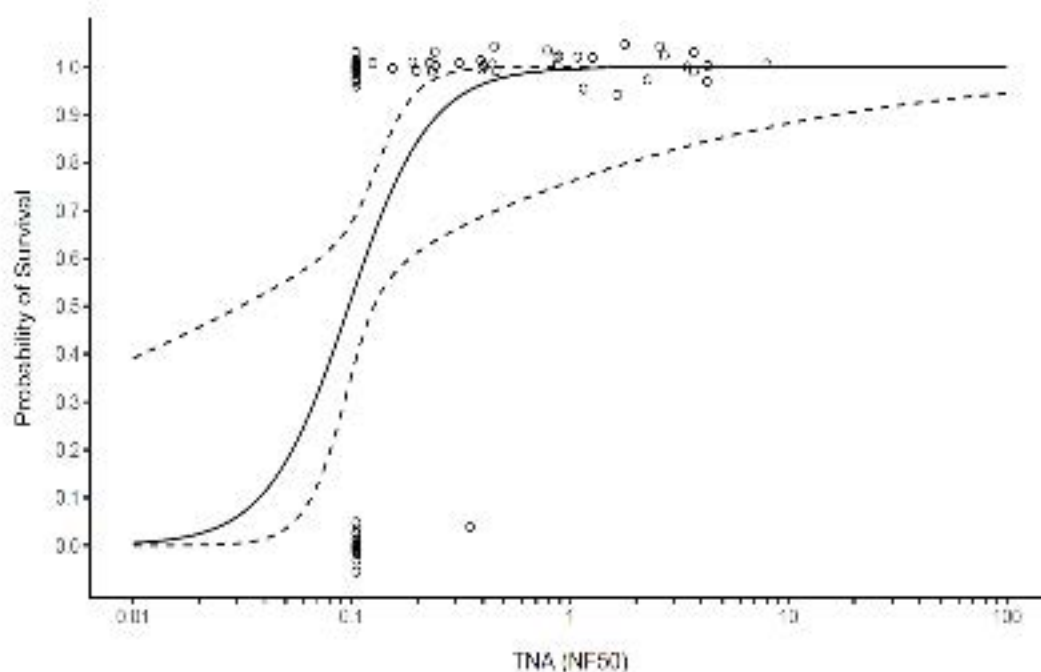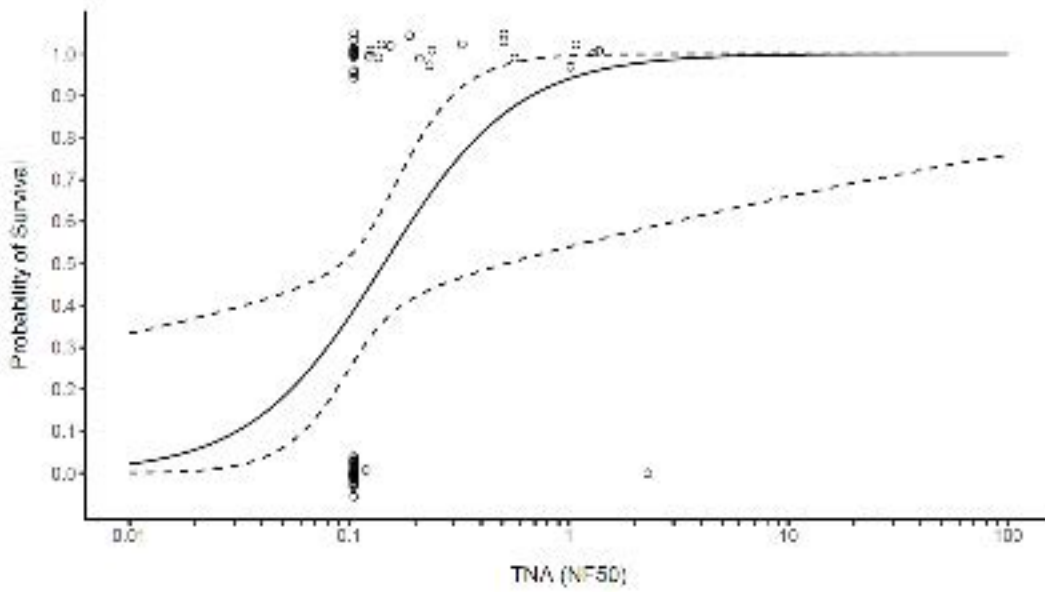
Figure 3   **Study 3655–100072763 Fitted Logistic Regression Model for Survival in the AV7909 Vaccinated Groups (9–14) as a Function of Log_{10} TNA NF$_{50}$ on Study Day 70–Challenge Day 70**

3. Example SAS program of PVE Calculation Using Kohberger Methodology with Double-Bootstrap Method

```
/***********************************************************************/
/* Program author:    Wendy Yin (08MAR2019) from EBS                   */
/* Program Purpose:   PVE Calculation Using Kohberger Methodology with */    /*
Double-bootstrap Method for Study AVA.212          */
/* Data step: The data set for this calculation will include animal data  */ /*
(setting =1,2) and clinical data (setting =3,4) with three      */
/*          variables used in the analysis: setting,survive(1=animal      */ /*
survive,0=animal death,and missing for human data) and          */ /*
log10nf50.                                                       */
/*     1. Generate animal data                                         */
/*          SEND Data source:    DM, DD, and LB in NHP Study 3655      */
/*          Population:          Group 1-6, NF50 at Day 28;            */
/*                               Group 9-14, NF50 at Day 70.           */
/*          Handling of LOQ NF50: NF50 LOQ = 0.105, non-missing value < LOQ is*/ /*
replaced with LOQ.                     */
/*          Need to create the following variables for analysis:      */
/*          Setting: 1= Group 1-6, NF50 at Day 28.                     */
/*                   2= Group 9-14, NF50 at Day 70 in Study 3655       */
/*          survive: 1= survive, 0 = death                             */
/*          log10nf50 = log10(NF50).                                   */
/*     2. Generate clinical data                                       */
/*          SDTM data source:    DM, DD, IS in AVA.212                 */
/*          Populations:         Per protocol population with study group */
/*                               AV7909 Lot 1 to 3.                    */
/*          Handling of LOQ NF50:  NF50 LOQ = 0.064, non-missing value<LOQ is */ /*
replaced with 1/2*LOQ =0.032          */
/*          Need to create the following variables for the analysis:   */
/*          Setting: 3 = NF50 records at Study Day 29,                 */
/*                   4 = NF50 records at Study Day 64.                  */
/*          log10nf50 = log10(NF50).                                   */
/*     3. Set animal data and clinical data into one data set.         */
/* PVE Calculation procedure:                                          */
/*     1. Resample analysis data set with replacement with setting as strata  */
/*     2. For resampled data,fit a logistic regression model to the animal    */ /*
(NHP) survival data (event = 'Y = 1') with TNA NF50 values (log      */
/*          transformed) as predictor X.                               */
/*          Firth option is used in the logistic model to handle the quasi-    */
/*          complete separation.                                       */
/*     3. Using the parameter estimates from logistic regression model in step*/ /*
2 and human TNA NF50 results to estimate the probability of survival*/
/*          for subject i, where xi is a log-transformed TNA NF50 value for    */
/*          subject i at Day 64 (or Day 29 for early protection).      */
/*     4. Calculate the mean of probability of survival.               */
/*     5. Repeat steps 1-4 for 1000 times.                             */
/*     6. Rank the resulted 1000 bootstrap predicted VE values from smallest  */ /*
to largest. The 2.5% and 97.5% percentiles are taken to be the 95%  */ /*
confidence interval for the predicted VE                        */
/***********************************************************************/;


ods listing close;
/***********************************************************************/
/* Use animal survival and NF50 data (setting = 2)to fit logistic regression */
/* Calculate pv with clinical NF50 (setting = 4)                       */
```

```
/* Calculate the mean of pv                                                  */
/****************************************************************************/
%macro onestepObsPred(datain=, setting=);
    %do i = 1 %to 2;
        %let sett=%scan(&setting., &i., %str(|));
        data Nsett&sett.;
          set &datain.;
            where setting=&sett.;
        run;

        %if &i = 1 %then %do;
            proc logistic data= Nsett&sett. outest=coeff;
              model survive(event='1')=&var. / firth;
            run;

            data _null_; set coeff;
                call symput("Intercept", strip(put(Intercept, 20.5)));
                call symput("slope",     strip(put(&var., 20.5)));
            run;
        %end;

        %if &i = 2 %then %do;
            data Nsett&sett.; set Nsett&sett.;
                xbeta = &Intercept.+&slope.*&var.;
              prob  = exp(xbeta)/(1+exp(xbeta));
                run;

            proc means data=Nsett&sett. noprint;
              var prob;
              output out=survival&i.(keep=pr&sett.)  mean=pr&sett.;
            run;

            data survival&i.(drop= pr&sett. ); set survival&i.;
                    pred&sett.=round(100*pr&sett., 0.1);
              format pred&sett. 6.1;
            run;
        %end;
    %end;

    %if &nsetting. =2 %then %do;
        data survival; set survival2; run;
    %end;
%mend;


/****************************************************************************/
/* Confidence interval from bootstrap data set                            */
/* Ti is a data set with &boot rows of point estimates of resampled data */
/****************************************************************************/
%macro conf_int(Tb, var, cl=0.95);
%put var=&var.;
  proc sort data=&Tb; by &var.; run;
  data CI&i(keep=Var CI);
    length Var $ 12 CI $ 20;
    format lowcl upcl 5.1;
    set &Tb;
```

```
      by &var.;
      if _n_=1 then do;
          index&var.=0;
          retain lowcl         upcl;
      end;
      index&var.+1;
      alpha=(1-&cl)/2;
      k_&var.=floor((&totalLoop.+1)*alpha);
      if index&var.=k_&var. then lowcl=&var.;
      if index&var.=&totalLoop.+1-k_&var. then upcl=&var.;
      if index&var.=&totalLoop. then do;
          Var="&var.";
          CI='('||strip(lowcl)||', '||strip(upcl)||')';
          output;
      end;
   run;
%mend;


/* Double-bootstrapping procedure */
%macro bstrap(setting=, totalLoop=);

%do loop =1 %to &totalLoop.;
    proc surveyselect data=&datain. out=resamp&dsn. NOPRINT
           seed=&loop. method=urs sampsize=samps outhits;
      strata setting;
    run;

    %onestepObsPred(datain=resamp&dsn.,setting=&setting.);

    %if &loop. =1 %then %do;
        data Tb&dsn.; set survival; run;
    %end;

    %if &loop. >1 %then %do;
        data Tb&dsn.; set Tb&dsn. survival; run;
    %end;
%end;

proc contents data=Tb&dsn. ;
  ods output variables=varname;
run;

proc sql;
  select variable into: varlist
     from varname;
quit;
%put &varlist;
%let nvar = %sysfunc(countw(&varlist., %str(|)));
%do i=1 %to &nvar.;
    %let var=%scan(&varlist., &i., %str(|));
    %conf_int(Tb=Tb&dsn., var=&var.);
%end;

data CI&dsn.;
  set CI:;
```

```
run;

proc transpose data=CI&dsn. out=CI&dsn.2 prefix=CI;
   var CI;
   id Var;
run;
%mend;


/**************************************/
/* Include all steps into this macro */
/**************************************/
%macro obspredTable(datain=, var=, setting=, totalLoop=2000);

  /* Clean data as needed */
   proc datasets; save &datain resamp: obs: parames:; quit; run;
   %let nsetting = %sysfunc(countw(&setting., %str(|)));
   %let dsn = %sysfunc(compress(&setting., %str( |)));
   %put nsetting=&nsetting;
   proc sql;
   create table samps as
     select setting, count(*) as _NSIZE_
       from &datain.
       group by setting
       order by setting;
   quit;

   %onestepObsPred(datain=&datain., setting=&setting.);

   data parames&dsn.; set survival; run;
   proc datasets; save &datain samps resamp: obs: parames:; quit; run;

   %bstrap (setting=&setting., totalLoop=&totalLoop.);

   %let spe1=%scan(&setting., 1, %str(|));
   %let spe2=%scan(&setting., 2, %str(|));
   data obs&dsn.;
     length spe1 spe2 8. pred $20;
     merge parames&dsn. ci&dsn.2;
     spe1=&spe1;
     spe2=&spe2;
     pred=strip(pred&spe2)||strip(CIpred&spe2);
     output;
   run;
%mend;
%obspredTable(datain=&data., var=log10nf50, setting=2|4, totalLoop=1000);
ods listing;
/*** End of the SAS code ***/
```

APPENDIX III   DUPLICATE SUBJECT ENROLLMENT AT DIFFERENT SITES SDTM DATA HANDLING

DESCRIPTION:

The following 8 subjects have been identified as being the same subjects that enrolled in 2 different sites, meaning only 4 unique subjects should be presented in the SDTM as per SDTM Implementation Guide version 3.2:

No. Unique Subjects	Subject ID	Site No.	Site Location	Age /Sex/Race	Date of Randomization	Number of Vaccination Received
1	US1022-0062	US1022		54/Female/Black	04/12/2019	3
	US1007-0003	US1007			04/29/2019	2
2	US1022-0072	US1022		40/Male/ Black	04/19/2019	3
	US1007-0029	US1007			05/01/2019	2
3	US1020-0030	US1020		28/Male/ Asian	04/05/2019	3
	US1005-0072	US1005			04/17/2019	3
4	US1005-0062	US1005		52/Male/White	04/08/2019	3
	US1020-0097	US1020			05/22/2019	1

Duplicate subject data will be handled on an SDTM level by reconciling the subject information under a single unique subject number as per Good Clinical Practices (GCP) and to capture the second enrollment DM information for the applicable subjects in supplemental variables including previous randomization and arm assignments.

One unique subject number derived from the first enrollment will remain in all domains for these subjects. The first randomization is the primary observation kept in the SDTM.DM domain for each affected subject. The Subject ID associated with the initial randomization will be used to identify these subjects.

Further action required:

Below is the implementation plan for the impacted domains:

In SDTM.DM domain, only the DM record from the first enrollment should be submitted for these four subjects who had two enrollments. The Supplemental Qualifiers dataset SUPPDM will be used to provide additional information from the second enrollment. The planned arm variable ARM should be populated with arm assigned in the first enrollment. The actual arm variable, ACTARM, should be populated with the treatment that the subject received in the first enrollment. Additional Supplemental Variables includes ARM1, ARMCD1, ACTARM1, ACTARMCD1 and RFSTDTC1.

The method of programming the above-mentioned will be via hard coding, this will be done in line with the IQVIA standard hardcoding process and will be implemented in accordance with IQVIA Dual programming process of validation. The Usual QC steps would be followed as per the CS_WI_BS015 Revision 12 Work Instruction.

For all other impacted domains (AE, CE, CM, CO, DA, DD, DS, DV, FA, FACE, HO, IE, IS, LB, MH, PE, RP, SS, VS) observations for both USUBJID's will be re-assigned to the Primary USUBJID and the duplicate Subject number will be populated in the SUBJID1 field. For records associated with the duplicate subject records mentioned in this document the --GRPID will be populated as "DUPENR". The --GRPID for Records associated with the initial enrollment will not have an assigned --GRPID.

The above-mentioned process will be done in a similar fashion as re-screening where a merge with the Demographics Domain (DM) will be done to determine if the subject had a duplicate enrollment, if true the USUBJID will be remapped based on the DM domain information.

For SE and SV all records from both the original and duplicate enrollment will be retained, these will be differentiated by means of the --GRPID variable populated as "DUPENR" to clearly distinguish the duplicate associate records from the original enrolment records. Example:

USUBJID	SESEQ	ETCD	ELEMENT	SEGRPID	EPOCH	SESTDTC	SEENDTC
EBS.AVA.212/US1001-0001	1	SCRN	Screening		SCREENING	2019-03-21	2019-03-21
EBS.AVA.212/US1001-0001	1	SCRN	Screening	**DUPENR**	SCREENING	2019-04-01	2019-04-01

For EX and EC the treatment arm information will be derived from either the main SDTM DM DOMAIN for non-duplicate subjects or from the supplemental variables for the duplicate subjects. This means that in EX and EC a subject may belong to 2 different treatment arms if the duplicate enrolled subject received treatment.

APPENDIX IV   DUPLICATE ENROLLMENT AT DIFFERENT SITES ADAM DATA HANDLING

DESCRIPTION:

The following 4 individuals enrolled under two separate subject numbers at 2 different sites, meaning only 4 unique subjects should be present in the SDTM data as per SDTM Implementation Guide version 3.2:

No. Unique Subjects	Subject ID	Site No.	Site Location	Age /Sex/Race	Date of Randomization	Number of Vaccination Received
1	US1022-0062	US1022		54/Female/Black	04/12/2019	3
	US1007-0003	US1007			04/29/2019	2
2	US1022-0072	US1022		40/Male/ Black	04/19/2019	3
	US1007-0029	US1007			05/01/2019	2
3	US1020-0030	US1020		28/Male/ Asian	04/05/2019	3
	US1005-0072	US1005			04/17/2019	3
4	US1005-0062	US1005		52/Male/White	04/08/2019	3
	US1020-0097	US1020			05/22/2019	1

Subjects will be combined into one unique identifier on an SDTM level by reconciling the subject information under a single unique subject number as per the SDTM Implementation Guide and to capture the second enrollment DM information for the affected subjects in supplemental variables including previous randomization and arm assignments.

The subject number associated with the first enrollment will remain in all domains as the USUBJID value for these subjects. The first Randomization is the primary observation kept in the SDTM.DM domain for each affected subject.

Further action required: The implementation plan for all domains in the ADaM datasets is outlined below:

ADSL

- ### Identifier variables:

USUBJID will be unique for all the subjects. For subjects with multiple enrollments, USUBJID at the first enrollment will be maintained in ADSL and the rest of the ADaM files. Nonetheless, SUBJID1 will be added and equal to the SUBJID assigned at the second site. In addition to ID, COUNTRY and STUDYID from first enrollment will be the same for both enrollments. However, SITEID for the second site will be mapped to SITEID1. For randomization by site table, subjects will be counted in the site at the first enrollment, with a footnote to clarify this convention; a listing will be generated to display the individual subject number, site number, and randomized treatment assigned to the two individual subject identifiers used for enrollment for these subjects.

- ### Demographic variables

Age-related variables, race, sex and baseline characteristics from the first enrollment will be used in demographic and baseline characteristics analysis.

- ### Population indicator variables

Data from the first enrollment will be used to derive safety, intent to treat, randomized, and screened population flags. Subjects with multiple enrollments will not be included in the Per Protocol population due to vaccinations received at both sites. In addition to these, 12-month safety follow-up completers will be based on the first enrollment.

- ### Treatment variables

Treatment-related variables will be mapped from ARM and ACTARM in DM domain. Treatment start/end date and treatment exposure are based on treatments received in the first enrollment. These four subjects received all the three vaccinations in the first enrollment. Vaccinations at the 2nd enrollment will be addressed in the CSR. The only display to include the second treatment, including exposure and compliance variables will be in the proposed listing for these four individuals. The start date/time of treatment associated with the second randomization will be used to identify which records are to be excluded from the planned analysis.

- ### Trial experience variables

These subjects were terminated from the 2nd enrollment site as soon as their multiple enrollments were confirmed. These subjects are being followed up at the first site until the end of study. Therefore, participant status should be based on the first enrollment. Variables related to trial status, in terms of visits and subject completion/termination, will be based on data associated with the first subject number randomized.

- ### Miscellaneous

Start date for second enrollment variable (date subject was screened at second site) and start of treatment associated with the second enrollment, and termination date associated with the second enrollment will be retained under unique variables within ADSL. Associated completion/termination dates maybe added as well.

ADVS, ADPE, ADLB, ADFACE

Data in these domains that were collected up to the start of the second enrollment are valid per protocol and will be included in the summary tabulations. However, data collected after second enrollment will be excluded from summary tabulations to maintain subject visit hierarchy. To accomplish this, derivation of the analysis flag will only consider observations prior to the start date of second enrollment.

ADIS

Refer to Population indicator variables in ADSL.

ADEX

Refer to Treatment variables in ADSL.

ADAE

All adverse events experienced during the study period in both enrollments will be included in the summary tabulations. All AEs on or after the start date of treatment in the first enrollment will be considered as treatment emergent. It is worth noting that AEs maybe reported under both subject numbers, but this will not impact incidence tables when the verbatim terms provided at the individual sites code to the same preferred term.

ADCM

All medications taken during the study period in both enrollments will be included in the summary tabulations. Prior medications will be those taken 30 days prior to start date of the first treatment associated with the first enrollment while concomitant medications will be those taken on or after the start date of the first treatment during the first enrollment. Note that medications can be reported under both subject numbers, but this will not impact incidence tables when the reported medications provided at the individual sites are coded to the same preferred name.

ADMH

Medical history data reported for either subject number will be included in summary tabulation unless the start date for the second enrollment clearly identifies that the history began after the first treatment of the first enrollment. An analysis flag will be added to flag only medical history which can contribute to the analysis.

ADDV

All protocol deviations experienced during the study period associated with either enrollment will be included in the summary tabulations.

ADSS

Refer to Population indicator variables in ADSL.

ADDD, ADIE

No impact on analysis.