STATISTICAL ANALYSIS PLAN
PHASE II

VERSION: 2.0
DATE OF PLAN:

APRIL 11, 2019

BASED ON:

Protocol V2.0

CRF V2.0

STUDY DRUG:

BioThrax®

AV7909

PROTOCOL NUMBER:

BP-C-17001

STUDY TITLE:

Randomized, Active-Comparison, Double-Blind, Phase 2 Study to Assess the Safety and Immunogenicity of Anthrax Vaccine Adsorbed (BioThrax®) without and with CPG 7909 Adjuvant (AV7909 Anthrax Vaccine), Using a Post Exposure Prophylaxis Dosing Regimen in Adults 66 Years of Age or Older in Stable Health in Comparison to Adults 18 50 Years of Age in Stable Health

SPONSOR:

Biomedical Advanced Research and Development Authority (BARDA)

[redacted]

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

This document has been reviewed and accepted by:

[redacted] Rho	Signature	Date
[redacted] Biomedical Advanced Research and Development Authority (BARDA)	Signature	Date

Document History

Version	Date	Change(s)	Author
1.0	28 Jun 2018	Initial Version	[redacted]
2.0	11 Apr 2019	Added definitions for seroconversion using TNA ED50 and ELISA anti-PA IgG; replace LLOD/ULOD with LLOQ/ULOQ; updated IPPP population protocol deviation criteria; added modified IPPP and corresponding analyses; added a column for MIPPP visit windows; deleted imputation methods for immunogenicity data; fixed minor grammatical errors; added exploratory immunogenicity comparisons; added AE tables by dose; modified blinding of AE and other tables for interim analysis; added solicited systemic reactogenicity symptoms by relationship tables; updated wording of safety and IFAP populations to include incorrectly randomized subjects; updated list of interim analysis tables; added clarification of SMC interim report; added criteria for using low level term instead of preferred term for some events	[redacted]

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1. LIST OF ABBREVIATIONS

Abbreviation	Term
ADaM	Analysis Data Model
AE	adverse event
ATC	Anatomical Therapeutic Chemical
AV7909	AV7909 Anthrax Vaccine
BARDA	Biomedical Advanced Research and Development Authority
BMI	body mass index
B-SAFE	BARDA Securing Anthrax Immunity For the Elderly
CI	confidence interval
CSR	Clinical Study Report
DOB	date of birth
DSMP	Data Safety Monitoring Plan
ECG	electrocardiogram
eCRF	electronic case report form
ED_{50}	effective dilution resulting in 50% neutralization
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
GM	geometric mean
H_0	null hypothesis
H_A	alternative hypothesis
HbA1C	hemoglobin A1C
HBV	hepatitis B vaccine
HCV	hepatitis C vaccine
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
hs-CRP	high-sensitivity C-reactive protein
ID	identification number
IFAP	immunogenicity full analysis population
IgG	immunoglobulin G
IM	intramuscular
IP	investigational product

IPPP	immunogenicity per protocol population
LLOQ	lower limit of quantitation
MAAE	medically attended adverse event
max	maximum
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities Terminology
min	minimum
MIPPP	modified immunogenicity per protocol population
NF_{50}	50% neutralization factor
OC	observed cases
PA	protective antigen
PIMMC	potentially immune-mediated medical condition
PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SCR	seroconversion rate
SD	standard deviation
SDTM	Study Data Tabulation Model
SI	International System of Units
SMC	Safety Monitoring Committee
SOC	system organ class
SPR	seroprotection rate
TNA	toxin neutralization antibody
ULOQ	upper limit of quantitation
WHO	World Health Organization

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the interim analysis and Clinical Study Report (CSR) for Protocol BP-C-17001. Additionally, this document provides details on study populations and on how the variables will be derived, how missing data will be handled as well as details on statistical methods to be used to analyze the safety and immunogenicity data

All decisions regarding final analysis, as defined in this SAP document, will be made prior to Database Freeze (unblinding) of the study data. Further information can be found in the protocol.

Deviations from the final approved SAP will be noted in the CSR.

If additional analyses are required to supplement the planned analyses described in this SAP, they will be identified in the CSR. Table, figure, and listing specifications are provided in separate documents.

3. STUDY OBJECTIVES

3.1. Primary Objectives

3.1.1. Safety

- To evaluate safety and reactogenicity, as determined by solicited local and systemic reactogenicity symptoms (within 8 days after each vaccination, inclusive of the vaccination day, excluding reactogenicity on the contralateral arm), of BioThrax or AV7909 administered to adults ≥66 years of age.

3.1.2. Immunogenicity

- To evaluate the seroprotection, defined as toxin neutralization antibody (TNA) 50% neutralization factor (NF_{50}) ≥0.56, rate at Day 64 for BioThrax or AV7909 administered to adults ≥66 years of age.

3.2. Secondary Objective

3.2.1. Safety

- To evaluate the occurrence of treatment-emergent unsolicited adverse events (AEs) (defined as all AEs other than solicited local and systemic reactogenicity symptoms), serious adverse events (SAEs), and medically attended adverse events (MAAEs), including potentially immune-mediated medical conditions (PIMMCs) from the time of the first dose of study investigational product (IP) through 12 months following the last dose of study IP.
- To evaluate the occurrence of solicited local reactogenicity symptoms on the contralateral arm (within 8 days after each vaccination, inclusive of the vaccination day).

3.2.2. Immunogenicity

- To assess the TNA NF_{50} antibody levels, seroprotection rates, and seroconversion (defined as a ≥4-fold increase over baseline levels, or a ≥4-fold increase over the lower limit of quantitation [LLOQ] if the baseline value is < LLOQ) rates for each study group at each applicable timepoint through Day 394.
- To assess the TNA effective dilution resulting in 50% neutralization (ED_{50}) antibody levels and seroconversion rates (defined as a ≥4-fold increase over baseline levels, or a ≥4-fold increase over LLOQ if the baseline value is < LLOQ) for each study group at each applicable timepoint through Day 394.
- To assess the enzyme-linked immunosorbent assay (ELISA) anti-protective antigen (PA) immunoglobulin G (IgG) antibody levels and seroconversion (defined as a ≥4-fold increase over baseline levels, or a ≥4-fold increase over LLOQ if the baseline value is < LLOQ) rates for each study group at each applicable timepoint through Day 394.

- To compare the TNA NF_{50} antibody levels, seroprotection rates, and seroconversion rates through Day 394 between younger adults (18 through 50 years) and older adults (≥66 years of age) within the following groups at each applicable timepoint:
    1. BioThrax given at Days 1, 15, and 29
    2. AV7909 given at Days 1 and 15 and placebo given at Day 29
- To compare the TNA ED_{50} antibody levels and seroconversion rates through Day 394 between younger adults (18 through 50 years) and older adults (≥66 years of age) within the following groups at each applicable timepoint:
    1. BioThrax given at Days 1, 15, and 29
    2. AV7909 given at Days 1 and 15 and placebo given at Day 29
- To compare the ELISA anti-PA IgG antibody levels and seroconversion rates through Day 394 between younger adults (18 through 50 years) and older adults (≥66 years of age) within the following groups at each applicable timepoint:
    1. BioThrax given at Days 1, 15, and 29
    2. AV7909 given at Days 1 and 15 and placebo given at Day 29

4. STUDY DESIGN

This is a phase 2, randomized, active-controlled, double-blinded, multi-site study to assess the safety and immunogenicity of BioThrax and AV7909 using a PEP dosing regimen in adults ≥66 years of age in stable health. The safety and immunogenicity profile of BioThrax and AV7909 in adults ≥66 years of age will also be compared to the safety and immunogenicity profile of subjects 18 through 50 years of age in stable health. The main study goal is to determine optimal dosing for AV7909.

Approximately 300 male and nonpregnant female adults (200 aged ≥66 years and 100 aged 18 through 50 years, inclusive) will be enrolled in the study.

After screening, subjects meeting all of the inclusion criteria and none of the exclusion criteria will be randomized to receive either BioThrax or AV7909. Randomization will be stratified by sex and age (18-50, 66-74, and ≥75 years). Subjects ≥66 years of age will be randomized 1:1:1:1 within stratum across 4 treatment arms (approximately 50 subjects per group), and subjects 18 through 50 years of age will be randomized 1:1 within stratum across 2 treatment arms (approximately 50 subjects per group) as specified in Table 1. Once randomized, subjects will receive 3 IP administrations, each separated by approximately 14 days, on Day 1, Day 15, and Day 29, based on their assigned treatment arm.

Table 1: Study Groups

Study Group	Number of Subjects	Age Group	Arm	Investigational Product	Route	Dose 1 Day 1	Dose 2 Day 15	Dose 3 Day 29
Group 1	50	Age ≥66	1	BioThrax	SC	BioThrax	BioThrax	BioThrax
Group 2	50	Age ≥66	2	AV7909	IM	AV7909	AV7909	AV7909
Group 3	50	Age ≥66	3	AV7909	IM	AV7909	AV7909	Placebo
Group 4	50	Age ≥66	4	AV7909	IM	AV7909	Placebo	AV7909
Group 5	50	Age 18-50	1	BioThrax	SC	BioThrax	BioThrax	BioThrax
Group 6	50	Age 18-50	3	AV7909	IM	AV7909	AV7909	Placebo

Note: SC = subcutaneous; IM = intramuscular

Immunogenicity assessments will include TNA NF_{50}, TNA ED_{50}, and ELISA anti-PA IgG antibody levels.

Safety assessments will be based on solicited AEs (local and systemic reactogenicity symptoms) occurring within 8 days of each IP administration, treatment-emergent unsolicited AEs occurring through Day 50, and treatment-emergent SAEs, MAAEs, and PIMMCs throughout the study.

Safety for each subject will be assessed from the time of the first dose of IP through 12 months following the last dose of IP.

The expected study duration is approximately 14 months per subject.

4.1. Sample Size Justification

The sample size for this study is approximately 300 subjects: 200 subjects ≥66 years of age (older cohort) and 100 subjects 18 through 50 years of age (younger cohort). Approximately 50 subjects will be randomized into each of 6 study groups.

The proposed sample size for this study is based on previous experience with similar BioThrax studies in individuals aged 18 to 65 years. The previous studies had study arms of similar size that proved to be sufficient to allow the collection of meaningful data, especially with respect to local and systemic reactogenicity symptoms and antibody levels.

Though no hypothesis testing will be performed as part of the primary analyses, Table 2 and Table 3 show the probability of observing a safety event and statistical power to detect crossing a threshold in seroprotection rate, respectively, under a variety of hypothetical scenarios. Within each table, separate calculations are performed for each pooled group of interest.

Probabilities of detecting a safety event were calculated using the binomial distribution (Table 2).

Table 2: Probability of Observing at Least 1 Safety Event of Interest under Different True Event Rates

True Probability of a Safety Event of Interest	Per Study Group (N=50)	Pooled Study Groups (N=100)	Pooled ≥66 Years of Age Cohort (N=200)	Overall (N=300)
0.0001	0.005	0.010	0.020	0.030
0.005	0.222	0.394	0.633	0.778
0.01	0.395	0.634	0.866	0.951
0.02	0.636	0.867	0.982	0.998
0.05	0.923	0.994	>0.999	>0.999
0.1	0.995	>0.999	>0.999	>0.999

A lower bound of 40% is considered to be a meaningful threshold of success for the seroprotection rate for BioThrax[1]. Assuming a one-sided alpha level of 0.025, an exact binomial test was used to calculate the power to detect the lower bound of an exact 95% confidence interval (CI) about an observed seroprotection rate being ≥40%, using sample size and hypothetical true seroprotection rate scenarios shown in Table 3.

Table 3: Power for Detecting a Lower 95% Confidence Limit of ≥40% about an Observed Seroprotection Rate

Hypothetical True Seroprotection Rate (%)	Per Study Group (N=50)	Pooled Study Groups (N=100)	Pooled ≥66 Years of Age Cohort (N=200)	Overall (N=300)
50	0.240	0.460	0.782	0.926
60	0.766	0.973	>0.999	>0.999
70	0.988	>0.999	>0.999	>0.999
80	>0.999	>0.999	>0.999	>0.999

5. STUDY DURATION AND VISIT SCHEDULE

Subjects will receive 3 study IP administrations, separated by approximately 14 days, and will be followed for 12 months after their last IP dose. The expected study duration is approximately 14 months per subject.

6. CLINICAL ASSESSMENTS

6.1. Screening and Baseline Assessments

Screening and baseline assessments include:

1. Obtain informed consent
2. Inclusion/exclusion criteria assessment, including the following:
   - urine pregnancy test (for females)
   - urine drug screening
   - hemoglobin A1C (HbA1C) >7.0%
   - human immunodeficiency virus (HIV), hepatitis B vaccine (HBV) and hepatitis C vaccine (HCV) screening
3. Physical exam, including vital signs assessment
4. Medical history, medication use and immunization history (within 30 days of screening)
5. Blood and urine samples for clinical laboratory assessments (hematology, chemistry and urinalysis)
6. Blood samples for baseline immunogenicity assessment parameters
7. Autoantibody assay
8. High-sensitivity C-reactive protein (hs-CRP) assay (for subjects ≥66 years of age)
9. Electrocardiogram (ECG)

6.2. Post-Baseline Assessments

Post-baseline assessments include (not all are performed at each visit):

1. Inclusion/exclusion criteria assessment for subsequent IP administrations, including urine pregnancy test for females
2. Symptom-directed physical exam, including vital signs assessment
3. Changes in medication use and immunization use
4. Blood and urine samples for clinical laboratory assessments (hematology, chemistry and urinalysis)
5. Blood samples for post-baseline immunogenicity assessment parameters
6. Autoantibody assay
7. High-sensitivity C-reactive protein (hs-CRP) assay (for subjects ≥66 years of age)
8. ECG
9. AE/SAE/MAAE/PIMMC assessment
10. Diary dispensation and collection/review for AEs/SAEs/MAAEs/PIMMCs

11. Post-IP administration exam for local reactogenicity symptoms and vital signs

6.3. Final Evaluation or Early Termination Visit

Final evaluation assessments at Visit 13 (Day 394) include:

1. Changes in medication use and immunization use
2. Blood for post-baseline immunogenicity assessment parameters
3. ECG
4. AE/SAE/MAAE/PIMMC assessment

For subjects who discontinue study participation prior to Visit 10 (Day 64), an early termination visit will be performed. Assessments that are conducted at early termination visits include:

1. Symptom-directed physical exam, including vital signs assessment
2. Changes in medication use and immunization use
3. Blood and urine samples for clinical laboratory assessments (hematology, chemistry and urinalysis) if clinically indicated
4. Blood samples for post-baseline immunogenicity assessment parameters if within acceptable window for next expected study visit
5. Autoantibody assay
6. AE/SAE/MAAE/PIMMC assessment
7. Diary collection/review for AEs/SAEs/MAAEs/PIMMCs

7. DEFINITIONS AND CONVENTIONS

7.1. General Summary Table and Individual Subject Data Listing Considerations

The following analyses and reporting conventions will be used:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (%)." Percentages will be rounded to one decimal place. If n=0, then no percent will be shown. To ensure completeness, all summaries for categorical and discrete variables will include all categories, even if none of the subjects had a response in a particular category.
- Numeric variables will be summarized using n, mean, standard deviation (SD), median, minimum (min), maximum (max). The min/max will be reported at the same level of significance as original data. The mean and median will be reported at one more significant digit than the precision of the data, and SD will be reported at two more significant digits than the precision of the data.
- The median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.
- Test statistics including t, *z* and *F* test statistics will be reported to two decimal places.
- *P*-values will be reported to three decimal places if greater than or equal to 0.001. If less than 0.001, the value will be reported as "<0.001."
- All tables, listings, and figures will be presented in landscape orientation.
- Courier New 8-point font will be used for all tables and listings.
- Dates will be displayed as ddmmmyyyy (e.g., 24Jan2017).

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

Tables, listings, and figures will include all study groups.

Study groups will be presented in unblinded reports as shown below:

- Study Group 1: Age ≥66 Arm 1
- Study Group 2: Age ≥66 Arm 2
- Study Group 3: Age ≥66 Arm 3
- Study Group 4: Age ≥66 Arm 4
- Study Group 5: Age 18-50 Arm 1
- Study Group 6: Age 18-50 Arm 3

Arms 1 through 4 will be defined in the footnotes of the displays.

7.1.1. Imputation of Missing Data

There will be no methods of imputation used for missing data for the summaries or analyses of the primary and secondary endpoints. No imputation will be implemented for safety or immunogenicity endpoint analyses.

7.2. Calculations Using Dates

Study days for dates on or after Visit 1 (Day 1) will be calculated as:

$$Study\ Day = Date - Visit\ 1\ Date + 1$$

For dates prior to Visit 1 (Day 1), study days will be calculated as:

$$Study\ Day = Date - Visit\ 1\ Date$$

Total duration is calculated as:

$$Duration = End\ Date - Start\ Date + 1$$

Age (years) for randomized subjects at the time of Visit 1 (Day 1) will be calculated as an integer according to the following formula:

$$Age = Integer\ portion\ of\ \frac{Visit\ 1\ Date - Birth\ Date + 1}{365.25}$$

Age for screen failures will be based on the informed consent date as opposed to Visit 1 (Day 1) date.

7.3. Baseline

For data collected at both Screening and Visit 1 (Day 1) pre-IP administration, the baseline data will be defined as the latest non-missing value collected. Otherwise, if data are collected at only one of Screening or Visit 1 (Day 1), the collected value will be considered the baseline value for analyses.

7.3.1. Visit Windows Relative to the First Dose of Study Medication

The visit schedule and allowable visit windows are provided in Table 4. Relative target days and visit windows are generally based on the timing of Visit 1 (Day 1). Visits occurring within 2 weeks of the 2nd or 3rd IP administration are shown with both relative target days and visit windows based on Visit 1 (Day 1) and relative target days and visit windows depending on the actual IP administration day (in parentheses). Similarly, the Visit 13 relative target day and visit windows are based on both Visit 1 (Day 1) and on the actual date of the 3rd IP administration. For these visits, if an applicable IP administration does not occur, the relative target day and visit window will be based on the date of the 1st IP administration at Visit 1 (Day 1).

Table 4: Visit Schedule

Visit	Relative Target Day	Visit Window	Modified Immunogenicity Per Protocol Population Visit Window
Screening	Not Applicable	-14 – -1	-14 – -1
Visit 1 (1st IP Administration)	1	1	1
Visit 2 (≥66 years of age only)	3	2 – 4	2 – 4
Visit 3	8	8 – 10	8 – 10
Visit 4 (2nd IP Administration)	15	14 – 18	12 – 23
Telephone Visit 1	17 (Visit 4 + 2)	16 – 18 (Visit 4 + 2 ±1)	16 – 18 (Visit 4 + 2 ±1)
Visit 5	22 (Visit 4 + 7)	22 – 24 (Visit 4 + 7 -0/+2)	22 – 24 (Visit 4 + 7 -0/+2)
Visit 6 (3rd IP Administration)	29 (Visit 4 + 14)	28 – 32 (Visit 4 + 14 -1/+3)	26 – 37 (Visit 4 + 14 -3/+8)
Telephone Visit 2	31 (Visit 6 + 2)	30 – 32 (Visit 6 + 2 ±1)	30 – 32 (Visit 6 + 2 ±1)
Visit 7	36 (Visit 6 + 7)	36 – 38 (Visit 6 + 7 -0/+2)	36 – 38 (Visit 6 + 7 -0/+2)
Visit 8	43 (Visit 6 + 14)	41 – 44 (Visit 6 + 14 -2/+1)	41 – 44 (Visit 6 + 14 -2/+1)
Visit 9	50	48 – 52	48 – 52
Visit 10	64	61 – 67	61 – 72
Visit 11	85	82 – 88	82 – 88
Visit 12	181	167 –195	167 –195
Telephone Visit 3	366	359 –373	359 –373
Visit 13	394 (Visit 6 + 365)	380 – 408 (Visit 6 + 365 ±14)	380 – 408 (Visit 6 + 365 ±14)

Data from out-of-window visits will not be excluded from analyses.

Unscheduled visits may also occur throughout the study. Data from unscheduled visits will be included in listings but will generally not be included in tabular or graphical summaries. The one exception is if the unscheduled visit occurs during the allowable visit window of an expected study visit that is missed or where some or all immunogenicity data were not collected/not analyzable; any available immunogenicity data from the unscheduled visit will be included in the summary of the expected study visit.

Early termination visits may occur for any subject terminating the study prior to Visit 10 (Day 64). These visits will be summarized together in tabular summaries, and will be included in listings. As with unscheduled visits, immunogenicity data from early termination visits that occur within the allowable visit window of an expected study visit with some or all immunogenicity data missing will be included in summaries of the expected study visit.

7.4. Analysis Populations

7.4.1. Screen Failures

A screen failure is defined as any subject who gives written informed consent but is not randomized at Visit 1 (Day 1). In addition, all subjects who are screened and found eligible but are not randomized will be considered screen failures. Besides reporting the reasons for not meeting inclusion/exclusion criteria, screen failures will not be included in any other analyses.

7.4.2. Randomized Population

The randomized population will include all subjects who are randomized into the study, regardless of actually receiving an IP dose. Each subject will be analyzed as part of the study arm assigned/age group combination. If any subjects of age 18-50 years are randomized in error to either arm 2 or arm 4 (due to randomization into the stratum for age ≥66 years), those subjects will be included with the study group of subjects age ≥66 years that corresponds to the randomized arm.

7.4.3. Safety Population

The safety population will include all subjects who are randomized and receive at least 1 IP dose. Each subject will be analyzed as part of the study group corresponding to the actual study group for the applicable dose for individual dose summaries. For all other analyses by study group, each subject will be analyzed corresponding to the actual study group for the first dose. If any subjects of age 18-50 years are randomized in error to either arm 2 or arm 4 (due to randomization into the stratum for age ≥66 years), those subjects will be included with the study group of subjects age ≥66 years that corresponds to the randomized arm. The safety population will be used for all safety analyses.

7.4.4. Immunogenicity Full Analysis Population

The immunogenicity full analysis population (IFAP) will include all subjects who are randomized, received at least one IP dose, and have at least one determinate assay result at any post-vaccination visit. Each subject will be analyzed as part of the treatment and dosing schedule actually received, regardless of the treatment arm assignment. If any subjects of age 18-50 years are randomized in error to either arm 2 or arm 4 (due to randomization into the stratum for age ≥66 years), those subjects will be included with the study group of subjects age ≥66 years that corresponds to the randomized arm. The IFAP will be used only for analysis of seroprotection based on TNA NF_{50} antibody levels at Day 64 as a secondary analysis.

7.4.5. Immunogenicity Per Protocol Population

The immunogenicity per protocol population (IPPP) will include all subjects who meet the following criteria:

- Randomized
- Received a full dose of IP at Visit 1 (Day 1), Visit 4 (Day 15), and Visit 6 (Day 29) within protocol specified visit windows (- 1 day, +3 days) (see Table 4).
- Received the correct treatment as assigned by randomization at Day 1, Day 15 and Day 29.
- Have no major protocol deviations that may have an impact on immunogenicity assessments. These are identified by a review of all protocol deviations by BARDA prior to performing formal analyses and prior to database lock.
- Have Visit 10 (Day 64) visit in-window (see Table 4).
- Have determinate assay results at the Day 64 visit.

The IPPP will be used for all primary and secondary immunogenicity endpoint assessments.

7.4.6. Modified Immunogenicity Per Protocol Population

The modified immunogenicity per protocol population (MIPPP) will include all subjects who meet the following criteria [note that the only differences between the following criteria and the IPPP criteria involve visit windows around vaccinations and Visit 10 (Day 64)]:

- Randomized
- Received a full dose of IP at Visit 1 (Day 1), Visit 4 (Day 15), and Visit 6 (Day 29) within visit windows of 3 days before to 8 days after the expected visit date (see Table 4).
- Received the correct treatment as assigned by randomization at Day 1, Day 15 and Day 29.
- Have no major protocol deviations that may have an impact on immunogenicity assessments. These are identified by a review of all protocol deviations by BARDA prior to performing formal analyses and prior to database lock.
- Have Visit 10 (Day 64) within a visit window of 3 days before to 8 days after the expected visit date (see Table 4).
- Have determinate assay results at the Day 64 visit.

The MIPPP will be used to perform all primary and secondary immunogenicity endpoint assessments as secondary analyses.

8. DATA PRESENTATIONS AND DATA MANAGEMENT

8.1. Data Presentations

Tables, listings, and figures will be created to display summary and subject level data.

The plan for tabular presentations and analysis of the data, in general, is divided into three categories:

1. Baseline and demographic profile
2. Analyses of the primary, secondary and exploratory immunogenicity objectives
3. Safety and tolerability, including analyses of primary and secondary safety objectives

All datasets (Study Data Tabulation Model [SDTM] and Analysis Data Model [ADaM] datasets), tables, and listings will be created using SAS software version 9.3 or higher. Figures will be programmed using SAS or R version 3.4.1 or higher.

8.2. Data Management

Study centers will enter study data in an electronic data capture (EDC) system. Laboratory data analyzed by central laboratories (e.g., chemistry, hematology, urinalysis and immunogenicity assays) will be transferred to Rho and integrated into the SDTM datasets, but will not be included in the EDC system.

Refer to the Data Management Plan for information concerning the EDC system.

8.3. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

All tables and listings will be created using RhoTables™, a suite of compiled SAS macros created by Rho for the generation of data displays. For more information on programming and validation processes, please see the Statistical Validation Plan.

In general, each listing will be sorted by study group (sorted according to the order in Table 1), subject identification number (ID) and date. For listings involving another categorical variable (e.g. laboratory parameter), consideration will be made to group related results within each listing for ease of comparing data.

Tables will include columns for each study group (sorted according to the order in Table 1), by pooled age group (regardless of study group; i.e. separate summaries for 18-50 years and ≥66 years), by pooled study groups (regardless of age group) for arms 1 and 3, and an overall column.

Tables, listings, and figures will be numbered and ordered according to a decimal system consistent with the corresponding CSR section. All displays will specify the applicable analysis population.

9. SUBJECT ACCOUNTING AND DEMOGRAPHIC PROFILE OF SCREEN FAILURES

9.1. Subject Accounting by Treatment Group and Sex

The age, sex and race of screen failures will be included in the listing of eligibility criteria not met. Since screen failures will not be randomized, no treatment group will be reported for these subjects.

9.2. Subject Distribution by Site

Screen failures will not be summarized by site.

9.3. Screen Failures

Subjects who sign informed consent and are screened but found to be ineligible will be considered to be screen failures. In addition, all subjects who are screened and found eligible but are not randomized will be considered screen failures. The specific eligibility criteria not met will be listed for these subjects. They will be excluded from other data displays.

10. SUBJECT DISPOSITION

The study disposition of all randomized subjects will be summarized in tables and listings.

The numbers and percentages of subjects will be presented that meet the following criteria:

- Randomized
- Completed study
- Early termination from study

In summary tables, percentages will be based on all subjects randomized within the specific study group. Categories for early study termination reasons will be presented, and percentages will be based on all subjects terminating early from the study within the specific study group.

Visit completion will be presented in a table as counts and percentages, reporting the status of the visit (completed or missed) and the number of subjects with visits out of window per visit. A listing of subject visit completion status will be presented.

The counts and percentages of subjects qualifying for each analysis population will be presented by study group. Percentages will be based on all subjects randomized. The primary reason for exclusion from the IPPP and the MIPPP will also be summarized as counts and percentages. A listing of each subject and analysis population inclusion will be presented.

11. BASELINE SUBJECT DATA

11.1. Baseline Demographic and Physical Characteristics

Demographic and baseline physical characteristics will be listed. Summary statistics for demographic and baseline physical characteristics will be reported in tables for each analysis population. Summaries by site will also be reported. Demographic characteristics will be summarized based on data collected from the Screening visit and include age (years), race, ethnicity and sex.

Body weight (kg), height (cm) and body mass index (BMI) (kg/(m)^2) will be reported from the Screening Visit, rounded to 1 decimal place. If body weight is reported in pounds, the following formula will be used to convert to kg:

$$Body\ Weight\ (kg) = \frac{Body\ Weight\ (pounds)}{2.2}$$

If height is reported in inches, the following formula will be used to convert to cm:

$$Height\ (cm) = Height\ (inches) \times 2.54$$

BMI will be calculated automatically within the EDC system using the values of height and weight entered by clinical site staff, based on the following formula:

$$BMI = \frac{Weight\ (kg)}{(Height\ [m])^2}$$

11.1.1. Listing of Subject Inclusion and Exclusion Criteria

For subjects screened but found to be ineligible, specific inclusion criteria not met and exclusion criteria met will be listed. Additional listings that show specific inclusion criteria not met and exclusion criteria met upon reassessment prior to the 2nd or 3rd IP administration will also be produced.

11.2. Medical History and Medical Conditions Present at Entry

Medical history items will be coded according to a standardized thesaurus (Medical Dictionary for Regulatory Activities [MedDRA]; refer to the Data Safety Monitoring Plan (DSMP) for the applicable version). Frequencies and percentages of subjects with previous or current medical conditions or surgeries will be summarized by body system and study group. Data listings will be prepared. Potential body systems assessed include skin, HEENT (head, eyes, ears, nose and throat), respiratory, cardiovascular, gastrointestinal, endocrine/metabolic, genitourinary, neurological, blood/lymphatic, musculoskeletal, hepatic, allergies, and psychological/psychiatric.

11.3. Prior Medication History and Medications Present at Entry

Immunization history within 30 days prior to screening will be listed for all subjects, with vaccination type and date of vaccination.

Prior medication history will be summarized with concomitant medication summaries.

11.4. Screening Laboratory Data

HIV, HBV and HCV antibody collection date and results at screening will be listed for all subjects.

HbA1C results at screening will be listed for all subjects, with date and time of collection, reference ranges, abnormal flags and clinical significance indicators.

Urine drug test results at screening will be listed for all subjects, with date of collection and results for each test.

12. IMMUNOGENICITY

12.1. General Considerations

All primary, secondary and exploratory immunogenicity analyses will be performed on the IPPP and MIPPP separately, and the IFAP will be used only for the primary immunogenicity endpoint summaries as a secondary analysis.

Since all hypothesis tests are performed as part of the secondary analyses, all statistical inferences of immunogenicity endpoints are considered exploratory in nature, including unadjusted 95% CIs and unadjusted *p*-values as appropriate.

No formal statistical analyses for the primary and secondary endpoints will be adjusted by site or any other covariates. Exploratory analyses may use site as a covariate in models, in addition to other covariates that are deemed appropriate.

12.2. Statement of the Null and Alternate Hypotheses

There are no comparisons or hypotheses involved in the primary immunogenicity objective.

As supportive analyses of the primary immunogenicity objective, the specified success criterion for TNA NF_{50} antibody levels is that the 95% lower bound CI about the seroprotection rate (SPR) is greater than 40%. The following null hypothesis will be tested within each study group, combined age group, combined treatment arm, and overall:

1. H_o: SPR based on TNA NF_{50} antibody levels at Day 64 is less than or equal to 40%

   H_a: SPR based on TNA NF_{50} antibody levels at Day 64 is greater than 40%

For secondary objectives comparing antibody levels in a pairwise fashion between study groups, the following null hypotheses will be tested for each pairwise comparison at each timepoint where immunogenicity data are collected:

1. H_o: SPR based on TNA NF_{50} antibody levels in both groups are equal

   H_a: SPR based on TNA NF_{50} antibody levels differ between groups
2. H_o: seroconversion rate (SCR) based on TNA NF_{50} antibody levels in both groups are equal

   H_a: SCR based on TNA NF_{50} antibody levels differ between groups
3. H_o: SCR based on TNA ED_{50} antibody levels in both groups are equal

   H_a: SCR based on TNA ED_{50} antibody levels differ between groups
4. H_o: SCR based on ELISA anti-PA IgG antibody levels in both groups are equal

   H_a: SCR based on ELISA anti-PA IgG antibody levels differ between groups
5. H_o: TNA NF_{50} antibody levels in both groups are equal

   H_a: TNA NF_{50} antibody levels differ between groups
6. H_o: TNA ED_{50} antibody levels in both groups are equal

   H_a: TNA ED_{50} antibody levels differ between groups

7. H_o: ELISA anti-PA IgG antibody levels in both groups are equal

   H_a: ELISA anti-PA IgG antibody levels differ between groups

12.3. Subgroup Analyses

No subgroup analysis is planned.

12.4. Multiple Comparisons and Multiplicity

For all hypothesis tests, significance will be declared at the two-sided α=0.05 level. Due to the exploratory nature of secondary analyses, no adjustments will be made for multiple comparisons.

12.5. Analysis of the Primary Immunogenicity Endpoint

The primary immunogenicity endpoint for this study is seroprotection at Day 64 based on TNA NF_{50} antibody levels. Seroprotection is defined as TNA NF_{50} antibody $\geq$0.56.

The primary analysis for this endpoint is descriptive. The following summary statistics will be displayed:

- count of subjects with non-missing data at the visit
- count of subjects meeting criteria for seroprotection
- proportion of subjects meeting criteria for seroprotection
- 95% exact (Clopper-Pearson) CI corresponding to the seroprotection rate

In addition, SPRs and corresponding 95% CIs will be displayed graphically by study group on Day 64.

The supportive analysis of the primary immunogenicity objective will be analyzed using a one-sided one-proportion *z*-test.

P-values for the supportive analysis will be displayed.

If more than 10% of subjects in the IPPP population are seroprotected at Visit 1 (Day 1) based on TNA NF_{50} antibody levels, sensitivity analyses will be performed by repeating analyses described in this section excluding the subjects who are seroprotected at Visit 1 (Day 1).

12.6. Analysis of the Secondary Immunogenicity Endpoints

All secondary immunogenicity endpoints are listed below and will be analyzed according to Section 12.6.1.1 (antibody level endpoints) or Section 12.6.1.2 (seroprotection and seroconversion endpoints).

- TNA NF_{50} antibody levels at Days 1, 8, 22, 29, 36, 43, 50, 64, 85, 181 and 394
- TNA ED_{50} antibody levels at Days 1, 8, 22, 29, 36, 43, 50, 64, 85, 181 and 394
- ELISA anti-PA IgG antibody levels at Days 1, 8, 22, 29, 36, 43, 50, 64, 85, 181 and 394
- Seroprotection based on TNA NF_{50} antibody levels at Days 1, 8, 22, 29, 36, 43, 50, 85, 181 and 394

- Seroconversion based on TNA NF_{50} antibody levels at Days 8, 22, 29, 36, 43, 50, 64, 85, 181 and 394, defined as a ≥4-fold increase over baseline levels, or a ≥4-fold increase over the LLOQ if the baseline value is below the LLOQ.
- Seroconversion based on TNA ED_{50} antibody levels at Days 8, 22, 29, 36, 43, 50, 64, 85, 181 and 394, defined as a ≥4-fold increase over baseline levels, or a ≥4-fold increase over the LLOQ if the baseline value is below the LLOQ.
- Seroconversion based on ELISA anti-PA IgG antibody levels at Days 8, 22, 29, 36, 43, 50, 64, 85, 181 and 394, defined as a ≥4-fold increase over baseline levels, or a ≥4-fold increase over the LLOQ if the baseline value is below the LLOQ.

12.6.1. Presentation of the Secondary Immunogenicity Results

12.6.1.1. Antibody Levels

Each secondary immunogenicity endpoint measuring TNA NF_{50}, TNA ED_{50} and ELISA anti-PA IgG antibody levels will be summarized similarly.

Antibody levels with a value that is less than LLOQ will be imputed for antibody level analyses as ½ LLOQ.

The following summary statistics will be displayed by visit as applicable:

- count of subjects with non-missing data at the visit
- geometric mean (GM) antibody levels and corresponding geometric standard deviation (SD)
- back-transformed 95% CI based on the t distribution about the GM antibody level
- minimum and maximum values
- median, and 1st and 3rd quartile values

Study group summaries of GM antibody levels for TNA NF_{50}, TNA ED_{50} and ELISA anti-PA IgG antibody levels by visit will be plotted on the $\log_{10}$ scale with corresponding 95% CIs. The reverse cumulative distributions of GM antibody levels for TNA NF_{50}, TNA ED_{50} and ELISA anti-PA IgG antibodies at Visit 10 (Day 64) will also be plotted.

Hypotheses concerning the immunogenicity antibody levels will be tested using pairwise *t*-tests on $\log_{10}$ transformed antibody levels, and *p*-values, geometric mean ratios, and back-transformed 95% CIs of the difference in $\log_{10}$ antibody levels will be displayed.

12.6.1.2. Seroprotection and Seroconversion Rates

Each secondary immunogenicity endpoint involving seroprotection and seroconversion rates will be summarized similarly. The following summary statistics will be displayed by visit for each visit as applicable:

- count of subjects with non-missing data at the visit
- count of subjects meeting criteria for seroprotection or seroconversion

- proportion of subjects meeting criteria for seroprotection or seroconversion
- 95% exact (Clopper-Pearson) CI corresponding to the seroprotection or seroconversion rate

Hypotheses concerning the primary immunogenicity endpoint (seroprotection rate at day 64) will be tested with a one-sample binomial test.

Hypotheses concerning the comparison of SPR and SCR between different groups will be tested with a Fisher's exact test using the IPPP and MIPPP. Risk differences of comparisons will be displayed with corresponding 95% exact unconditional CIs (based on the Santner and Snell method) and *p*-values (based on two-sided Fisher's exact test).

A data listing of antibody levels will be prepared, which will include seroprotection (for TNA NF_{50} antibody levels only) and seroconversion status (for TNA NF_{50}, TNA ED_{50} and ELISA anti-PA IgG antibody levels separately) at each applicable visit.

12.7. Analysis of the Exploratory Immunogenicity Endpoints

12.7.1. Antibody level correlations

Correlations between 1) TNA NF_{50} and ELISA anti-PA IgG antibody levels and 2) TNA ED_{50} and ELISA anti-PA IgG antibody levels will be calculated at Visit 10 (Day 64). Pairwise scatter plots on the $\log_{10}$ scale with regression lines will be created. The Pearson correlation coefficient will be presented with corresponding *p*-value. This analysis will be performed on the IPPP and MIPPP.

12.7.2. Additional pairwise comparisons

The following pairwise comparisons of TNA NF_{50} antibody levels and seroprotection rates will be performed at the given visit using the hypothesis testing methodology stated in Section 12.6.1.1:

1. Group 1 vs. combined Groups 2 and 3 at Day 29
2. Group 1 vs. Group 3 at Day 64
3. Group 1 vs. Group 4 at Day 64
4. Group 5 vs. Group 6 at Day 29
5. Group 5 vs. Group 6 at Day 64

The hypotheses applicable to each pairwise comparison are the following:

H_o: TNA NF_{50} antibody levels (or seroprotection rates) in both groups are equal

H_a: TNA NF_{50} antibody levels (or seroprotection rates) differ between groups

These analyses will be performed on the IPPP and MIPPP by the treatment actually received.

13. SAFETY AND TOLERABILITY

13.1. Overall Summary of Tolerability

Only treatment-emergent AEs, those starting or worsening in severity on or after the first IP administration, are collected on the eCRF. AEs with missing start dates will be considered treatment-emergent.

All safety analyses will be carried out using the safety population defined in Section 3.1 unless otherwise noted. Missing safety information will not be imputed. These analyses will not be stratified by site or sex.

The following summaries of all AEs will be given for combined dose 1, dose 2 and dose 3, as well as individually for dose 1, dose 2 and dose 3:

- AEs by SOC and PT
- AEs by AE Type (Solicited or Unsolicited) and PT
- AEs by SOC, PT and maximum severity
- AEs by SOC, PT and relationship to IP
- AEs by SOC, PT and earliest days of onset
- The count of AEs and percentage of subjects experiencing AEs that fit the following categories:
    - AEs (overall and related to IP)
    - SAEs (overall and related to IP)
    - Severe AEs (overall and related to IP)
    - AEs leading to early termination of IP
    - AEs leading to study withdrawal
    - AEs leading to death
    - Solicited local reactogenicity symptoms (overall and severe)
    - Solicited local contralateral reactogenicity symptoms (overall and severe)
    - Solicited systemic reactogenicity symptoms (overall and severe)
    - PIMMCs (overall and severe)
    - MAAEs (overall and severe)
    - Unsolicited AEs (overall and severe)

13.2. Adverse Event Preferred Term and System Organ Class Summary Tables

All AEs will be classified by system organ class (SOC) and preferred term (PT), according to MedDRA. For solicited reactogenicity symptoms of injection site tenderness, the low level term will be used instead of preferred term to distinguish these symptoms from injection site pain, as

they are explicitly collected in subject diaries and vaccine site examinations. The severity and attribution of AEs will be classified by the investigator on the eCRF. Each AE is entered on the eCRF once at the highest severity.

13.2.1. Summaries of Adverse Event Incidence Rates for All Subjects

Separate summaries of solicited local and systemic reactogenicity symptoms and unsolicited AEs will be prepared for the following:

- combined dose 1, dose 2 and dose 3 (start dates occurring in the periods of Day 1 through 8, Day 15 through Day 22, and Day 29 through 36)
- dose 1 only (start dates occurring in the period of Day 1 through 8)
- dose 2 only (start dates occurring in the period of Day 15 through 22)
- dose 3 only (start dates occurring in the period of Day 29 through 36)

AEs beginning after the 1st IP administration on Day 1 and prior to the 2nd IP administration on Day 15 will be included in dose 1 summaries. AEs that begin prior to the 1st IP administration will only be included in dose 1 summaries if they worsen after IP administration. Similarly, AEs that start after the 2nd IP administration on Day 15 and prior to the 3rd IP administration will be included in dose 2 summaries. AEs beginning after the 3rd IP administration on Day 29 and prior to or on Day 50 will be included in dose 3 summaries.

For summaries of AEs, the count of events that fit the specified criteria will be presented.

The number of subjects experiencing at least one event will be described using counts and percentages per study group. Percentages will be based on the number of subjects in the safety population within the study group. For summaries of events associated with dose 2 or dose 3, percentages will be based on the number of subjects in the safety population within the study group who received the 2nd or 3rd IP administration, respectively.

The incidence of AEs will be summarized. If a subject experienced more than one episode of an AE, the subject is counted once for that PT. If a subject had more than one AE in a SOC (or AE type, if applicable), the subject is counted only once in that SOC (or AE type) according to the highest severity rating (in order, mild [grade 1], moderate [grade 2], or severe [grades 3, 4 and 5]). If the severity of the AE is not reported, then the severity of the AE will be counted as unknown. The summary tables will include incidence estimates for overall SOC (or AE type) as well as for PTs within each SOC (or AE type). Incidence will be presented alphabetically by SOC (or AE type) and then by PT within each SOC (or AE type) by decreasing frequency overall and then alphabetically.

The investigator is to record their opinion on the relationship of each AE to IP ("not related", "unlikely related", "possibly related", "probably related" and "related"). If a subject experiences the same AE multiple times, the event with the strongest relationship to IP will be counted. For summaries of IP-related AEs, the categories of "possibly related", "probably related" and "related" will be considered IP-related. If the relationship is missing, it will be counted as "related" in summaries.

Day of onset relative to the most recent IP administration will be dichotomized for summaries as ≤8 days post IP administration and ≥9 days post IP administration. If a subject experiences the

same AE multiple times for the same IP administration, the event with the closest start date to IP administration will be counted.

Solicited local reactogenicity symptoms and solicited systemic reactogenicity symptoms will be summarized by maximum severity with 95% exact (Clopper-Pearson) CIs for dose 1, dose 2, and dose 3, separately, and combined dose 1, dose 2 and dose 3. Solicited local reactogenicity symptoms on the contralateral arm will be summarized similarly for dose 2 and dose 3.

In addition, solicited systemic reactogenicity symptoms will be summarized by the strongest relationship to IP in the same method as described above.

Unsolicited adverse events will be summarized by maximum severity with 95% exact (Clopper-Pearson) CIs for dose 1, dose 2, and dose 3, separately, and combined dose 1, dose 2, and dose 3.

In addition, all AEs will be listed by subject in chronological order including ID, age, race, sex, and all related event status information (start and stop dates, whether the event was resolved, study day of onset, severity, seriousness, relationship to IP, action taken with IP, and outcome). Separate flags will be displayed for solicited local reactogenicity symptoms, solicited systemic reactogenicity symptoms, SAEs, PIMMCs, MAAEs, unsolicited AEs, deaths, AEs leading to treatment discontinuation, and AEs leading to subject study withdrawal. Additionally, a coding list of PTs and the verbatim text associated with them will be produced.

SAEs, MAAEs and PIMMCs will be summarized in tables and presented in separate listings.

13.2.2. Missing and Partial AE Onset Dates

The following conventions will be used for imputing missing start dates.

- For start dates that are missing the day value with non-missing month and year:
    - If the start year is the same as the year of Visit 1 (Day 1), then do the following:
        - If the start month is the same as the month of Visit 1 (Day 1), the start date will be imputed as the date of Visit 1 (Day 1).
        - If the start month is not the same as the month of Visit 1 (Day 1), then the start date will be imputed as the first day of the non-missing start month.
    - If the start year is not the same as the year of Visit 1 (Day 1), then the start day will be imputed as the first day of the start month.
- For start dates that are missing the day and month values with non-missing year:
    - If the start year is the same as the year of Visit 1 (Day 1), the start date will be imputed as the date of Visit 1 (Day 1).
    - If the start year is after the year of Visit 1 (Day 1), the start month and start day will be imputed as January 1.
- Completely missing start dates will be imputed as the date of Visit 1 (Day 1).

End dates will not be imputed.

13.2.3. Early Termination of Investigational Product due to Adverse Event, Subject Study Withdrawal due to Adverse Event, and Death

AEs leading to early termination of IP will be summarized in a table by SOC and PT and will be presented in listings. Similar summaries and listings will be provided for AEs leading to subject study withdrawal. AEs leading to death and potentially life-threatening (grade 4) AEs will also be listed.

13.3. Pregnancy Monitoring and Assessment

Urine pregnancy assessments will be done at Screening and prior to IP administration on Visit 1 (Day 1), Visit 4 (Day 15) and Visit 6 (Day 29). Date, time and result of each pregnancy assessment will be listed for all female subjects.

In the case of one or more pregnancies occurring during study participation, a data listing will be prepared to display applicable information, including date of report, method of pregnancy confirmation, delivery date (if applicable), pregnancy termination status and week (if applicable), and any problems or congenital abnormalities present.

13.4. Safety Endpoint Analyses

13.4.1. General Considerations

All statistical inferences of safety endpoints are considered exploratory in nature, including unadjusted 95% CIs.

13.4.2. Statement of the Null and Alternate Hypotheses

There are no comparisons or hypotheses involved in the primary or secondary safety objectives.

13.4.3. Subgroup Analyses

No subgroups will be analyzed. No by-site analyses are planned.

13.4.4. Analysis of the Primary Safety Endpoint

The primary safety endpoint for the study is all solicited local and systemic reactogenicity symptoms occurring within 8 days of each IP administration, inclusive of the IP administration day, excluding reactogenicity symptoms on the contralateral arm.

For the primary safety endpoint, a solicited local or systemic reactogenicity symptom is defined as any of the following occurring within 8 days after each IP administration, inclusive of the IP administration day, excluding reactogenicity symptoms on the contralateral arm:

- Solicited local reactions at the injection site: warmth, tenderness, itching, pain, restriction of range of arm motion, erythema/redness, palpable or observable lump, induration/swelling, and bruising
- Solicited systemic reactions: fatigue, myalgia/muscle ache, headache, and fever

Primary endpoint results will be summarized with frequency, percentage and 95% confidence interval, and displayed in tables described in Section 13.2.1.

13.4.5. Analysis of the Secondary Safety Endpoints

All secondary safety endpoints are listed below:

- All treatment-emergent unsolicited AEs. Unsolicited AEs are defined as all other than solicited local and systemic reactogenicity symptoms.
- All treatment-emergent SAEs occurring during study participation. SAEs are defined in Protocol Section 11.2.1.3.
- All treatment-emergent MAAEs occurring during study participation. MAAEs are defined as AEs with medically attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. AEs (e.g. abnormal vitals) identified at a routine study visit will not be considered MAAEs.
- All treatment-emergent PIMMCs that occur during study participation. PIMMCs are defined in Protocol Appendix 3.
- All solicited local reactogenicity symptoms on the contralateral arm occurring within 8 days after each vaccination, inclusive of the vaccination day.

Secondary endpoint results will be summarized with frequency and percentage, and displayed in tables described in Section 13.2.1.

13.4.6. Summary of Reasons for Safety Non-evaluability/Exclusion from Safety Analyses

All subjects who are randomized and receive at least 1 IP administration will be included in safety analyses. Therefore, a listing of screen failures will be considered the presentation of subjects excluded from safety analyses.

13.5. Investigational Product Administration Compliance

IP administration adherence for dose 1 at Visit 1(Day 1), dose 2 at Visit 4 (Day 15) and dose 3 at Visit 6 (Day 29) will be summarized and listed. Counts and percentages of subjects receiving any amount or a full amount of dose 1, dose 2 and dose 3, separately, will be reported in tables; the denominator will be the number of subjects within each group as randomized. For subjects who receive all 3 doses of IP, the counts and percentages of subjects receiving 3 doses of IP according to the correct study arm will be summarized. For subjects terminating IP administration early, the reasons for terminating IP administration early will also be presented. For subjects who received the first IP administration but are found ineligible for the second or third IP administration, specific inclusion and exclusion criteria not met at Visit 4 (Day 15) or Visit 6 (Day 29) will be listed separately.

Details of IP administration will be listed for each IP administration, including date of IP administration, time IP removed from storage/refrigerator, time of IP preparation, time of administration, location of administration and whether a full dose was received.

13.6. Concomitant and Other Medications

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary (refer to the DSMP for the applicable version). Medications reported on the eCRF will be

categorized for analysis as prior or concomitant to IP administration by comparing the medication start and stop dates with the first IP administration dates. Prior medications will have a medication start date prior to the first IP administration date. Concomitant medications will have a medication start on or after the first IP administration date or a stop date on or after the first IP administration date. Medications that fit the criteria for both a prior and concomitant medication will be indicated as such in data listings.

The number and percentage of subjects receiving prior or concomitant medications will be presented overall and by medication class. When reporting the number of subjects receiving the medication, a subject will only be counted once if they ever received the medication within the medication class.

Medication usage will be listed, including Anatomical Therapeutic Chemical (ATC) level 4 coding term, verbatim drug name, preferred drug name, start date, end date, dose (with unit), frequency, route, ongoing status and indication.

Non-IP immunizations will be collected post-Screening. Concomitant immunizations will be listed, including immunization type and date.

13.6.1. Missing and Partial Concomitant and Other Medication Start and Stop Dates

The following conventions will be used for imputing missing start dates.

- For start dates that are missing the day value with non-missing month and year:
    - If the start year is the same as the year of Visit 1 (Day 1), then do the following:
        - If the start month is the same as the month of Visit 1 (Day 1), the start date will be imputed as the date of Visit 1 (Day 1).
        - If the start month is not the same as the month of Visit 1 (Day 1), then the start date will be imputed as the first day of the non-missing start month.
    - If the start year is not the same as the year of Visit 1 (Day 1), then the start day will be imputed as the first day of the non-missing start month.
- For start dates that are missing the day and month values with non-missing year:
    - If the start year is earlier than the year of Visit 1 (Day 1), the start month and day will be imputed as July 1.
    - If the start year is the same as the year of Visit 1 (Day 1), the start date will be set to the date of Visit 1 (Day 1).
    - If the start year is after the year of Visit 1 (Day 1), the start month and start day will be imputed as January 1.
- Completely missing start dates will be imputed as the date of Visit 1 (Day 1).

End dates will not be imputed.

13.7. Investigational Product Administration Site Examination

Observations from the IP administration site post IP administration will be summarized by visit and study group. IP administration site examinations will be summarized separately for

locations of dose 1, dose 2 and dose 3. Dose 1 site examinations will occur on Visit 1(Day 1), Visit 2 (Day 3) (for ≥66 age group), Visit 3 (Day 8) and Visit 4 (Day 15); dose 2 site examinations will occur on Visit 4 (Day 15), Visit 5 (Day 22) and Visit 6 (Day 29); dose 3 site examinations will occur on Visit 6 (Day 29), Visit 7 (Day 36) and Visit 8 (Day 43). Counts and percentages of subjects experiencing warmth, tenderness, itching, pain, restriction of range of arm motion, erythema/redness, palpable or observable lump, induration/swelling, and bruising at the injection site will be presented. Summaries of the largest diameter of erythema/redness, and induration/swelling will be presented as well.

IP administration site examination information will also be listed for each subject, dose and visit. Information included will be IP administration date, date of examination, time of examination, days since IP administration, whether a photograph was taken of the abnormality, and all information summarized in IP administration site examination tables described above in this section.

13.8. Diary Card Measurements

Participant-reported diary card measurements of vaccinated and contralateral arm (if applicable) IP administration site erythema/redness and induration/swelling will be listed for each subject, dose and study day for 8 days post-IP administration.

13.9. Clinical Laboratory Data

Clinical laboratory measurements of serum chemistry, hematology and urinalysis will be performed at a central laboratory. All clinical laboratory data will be reported using the International System of Units (SI). If SI units are not available, laboratory-reported units will be used. Descriptive statistics of laboratory values will be presented by visit. Summaries of actual values and change from baseline values by visit will be presented for quantitative laboratory parameters (e.g., white blood cells, lymphocytes). Baseline is defined as the last lab value prior to IP administration.

If two or more evaluations occur in the same visit window, the latest evaluation will be selected for inclusion in the analysis.

Clinical laboratory results will receive a toxicity grade according to Protocol Appendix 2. Clinical laboratory results of grade 1 through 3 that are deemed by the investigator as being clinically significant will be recorded as AEs with a corresponding toxicity grade as described above and will be presented with the AE displays. All grade 4 laboratory values will be considered AEs.

Shift tables will be prepared to display cross-tabulations of the number of subjects experiencing each toxicity grade at baseline compared to other visits by clinical laboratory test.

All clinical laboratory values will be presented in a listing.

13.10. Vital Signs

Vital signs parameters of blood pressure (systolic and diastolic) (mmHg), pulse rate (beats/minute), respiratory rate (breaths/minute), oral temperature (°F), and oxygen saturation by pulse oximeter (%) will be summarized and listed for all visits with applicable data. For all

results collected post-baseline, change from baseline will be displayed. Visit 1 (Day 1) pre-IP administration vital signs results will be considered baseline for summaries of vital signs data. If the Visit 1 (Day 1) pre-IP administration result is missing, screening results will be considered baseline.

Toxicity grading of vital signs results according to Protocol Appendix 2 will be presented with vital signs displays. Vital signs results that are deemed by the investigator as being clinically significant will be recorded as AEs with a corresponding toxicity grade as described above and will be presented with the AE displays.

Shift tables will be prepared to display cross-tabulations of the number of subjects experiencing each toxicity grade at baseline compared to other visits by vital sign parameter.

All vital signs will be listed in by-subject listings including visit and collection date.

13.11. Physical Examination

Physical examinations will be performed, but only abnormal results will be recorded as either a medical history item at screening, or as an adverse event. Physical exam results will not be reported otherwise.

13.12. Other Safety Assessments

ECG test results will be collected at Screening, Visit 7 (Day 36) and Visit 13 (Day 394). Results will be reported in data listings, including visit and collection date.

High-sensitivity C-reactive protein (hs-CRP) assay results will be collected at Visit 1 (Day 1) and Visit 2 (Day 3) for subjects ≥66 years of age. Results will be reported in data listings, including visit and collection date.

Blood samples for autoantibody assays will be collected and frozen for potential testing at Visit 1 (Day 1), Visit 10 (Day 64) and at the early termination visit (if applicable) for subjects ≥66 years of age. If the samples are analyzed, results will be reported in data listings, including visit and collection date.

13.13. Subject Study Withdrawal Status

Reasons for subject study withdrawal will be included in the study disposition displays described in Section 10.

14. PROTOCOL DEVIATIONS

Protocol deviations captured in the eCRF, including site-level protocol deviations, will be listed by site with information such as type of deviation, severity of the deviation (major or non-major), date of occurrence, and the reason for the deviation. Protocol deviations will be summarized in tabular format by type of deviation.

15. MAINTAINING THE BLIND

For all analyses requiring unblinded data from study start through the Day 394 analysis for the final CSR, a blinded programming team consisting of programmers and statisticians will perform all programming tasks (including SDTM datasets, ADaM datasets, tables, listings, and figures) and all associated validation tasks using dummy study groups, which will be randomly assigned. After validation of datasets and displays using dummy study groups, an unblinded team of a statistician and a programmer will generate, interpret and report each analysis using appropriate study groups and will not modify any programs used to perform analyses.

Any necessary modification of programs due to incorrect coding will be communicated from the unblinded team to the blinded team so that the blinded team can modify the coding while being blinded to study groups, after which the unblinded team will then rerun analyses using unblinded data. This process is continued until the unblinded team ensures all data issues have been resolved.

15.1. Immunogenicity Data

Immunogenicity data of TNA NF_{50}, TNA ED_{50} and ELISA anti-PA IgG antibody levels may potentially be unblinding to study group, as a higher antibody level would be expected from subjects receiving active IP compared to placebo. To ensure that no blinded individual may be unblinded by viewing the immunogenicity data, the unblinded statistician will randomly reassign the IDs in the file so that antibody levels will be assigned to different subjects than those subjects to which they actually correspond. Blinded programming tasks will be done only on the reassigned file. The file with correct ID assignments will be used for all unblinded analyses and will only be viewable by unblinded individuals.

16. INTERIM ANALYSES

An interim analysis will be performed based on cumulative immunogenicity and safety data through Visit 10 (Day 64) for all subjects. At the interim analysis, the study database (all data through Visit 10 [Day 64]) will be monitored and cleaned per the Data Management Plan.

The blinding at the subject level will be maintained for those outside of the unblinded team until database lock of all data through Day 394 for the clinical study report. Blinding at the subject level will be maintained for the interim analysis as specified in Section 15.

All primary and secondary endpoint analyses will be performed for the interim analysis as specified in Sections 12.6 and 12.7 (for immunogenicity analyses) and Sections 13.4.4 and 13.4.5 (for safety analyses). Additional analyses included in the interim analysis, such as subject disposition and demographics, will be performed based on Sections 10 and 11. Exploratory immunogenicity analyses will also be included in the interim analysis.

In order to prevent unblinding of any individual subjects, tabular summaries of data will exclude extreme values (minimum and maximum). Listings will not be included in the interim analysis package. Immunogenicity tables and figures will report study group and pooled group statistics and counts. AE tables will not report study group specific counts, but will instead report the overall totals and totals by age group. As such AE tables will remain blinded, even at the group level. All remaining tables included in the interim analysis that may have small counts will not report study group specific counts for applicable variables.

The unblinded statistician will be responsible for reporting interim results to Biomedical Advanced Research and Development Authority (BARDA).

Since all active subjects will have completed Visit 10 (Day 64) and this timepoint is of primary interest, there will be no penalty for an early look at the data. In addition, no decisions regarding the status of the study will be made as a result of the interim analysis.

The interim analysis tables and figures will be a subset of the final tables and figures included in the CSR. At the time of the final analysis for the CSR, all tables and figures generated as part of the interim analysis will be regenerated to include data through the end of the study.

17. SAFETY MONITORING COMMITTEE MEETINGS

The Safety Monitoring Committee (SMC) will perform a planned review of interim safety data after 40 subjects ≥66 years of age have completed Visit 7 (Day 36). Enrollment and dosing will continue during this planned SMC review. In addition, ad hoc reviews will occur in the event that pausing/stopping rules are met or a review is deemed necessary by the SMC chair.

Following the planned interim analysis (described in Section 16), a final set of SMC data displays will be provided to the SMC members. These displays will be of the same format as provided for the planned SMC data review but will be run on the clean and frozen data from the interim analysis.

The blind will be maintained for all blinded individuals according to Section 15. The unblinded statistician will be responsible for presenting data to the SMC. Safety analyses for SMC review will be completed using the safety population.

Refer to the SMC Charter for more details of the SMC procedures and reporting.

18. CHANGES TO COMPLETED REPORTS

The study database will be monitored and cleaned per the Data Management Plan for all data through Visit 10 (Day 64) for the interim analysis and Visit 13 (Day 394) for the final CSR. In the event of any changes in the clinical database at the time of final database lock that affect information reported in the interim analysis, these changes will be noted in the CSR.

19. REFERENCES

1. BioThrax® (Anthrax Vaccine Adsorbed); Suspension for Intramuscular or Subcutaneous Injection [package insert]. Lansing, MI: Emergent BioDefense Operations Lansing LLC, 2015.

20. APPENDIX

20.1. Table of Contents for Data Display Specifications

Tables

Table Number	Table Title	Applicable Reports (I=Interim, C=Final CSR)	Applicable Populations (R=Randomized, S=Safety, F=IFAP, P=IPPP M=MIPPP)
Table 14.1.1.1	Subject Disposition by Study Group	I, C	R
Table 14.1.1.2	Visit Completion by Study Group	I, C	R
Table 14.1.1.3	Analysis Populations by Study Group	I, C	R
Table 14.1.2	Protocol Deviations by Study Group	C	R
Table 14.1.3.1	Demographics and Baseline Physical Characteristics by Study Group	I, C	S, F, P, M
Table 14.1.3.2	Demographics and Baseline Physical Characteristics by Site and Study Group	C	S, F, P, M
Table 14.1.4	Medical History by Study Group	C	S
Table 14.1.5	Concomitant Medications by System Organ Class, Preferred Term and Study Group	C	S
Table 14.1.6	Investigational Product Administration Adherence by Study Group	I, C	S
Table 14.2.1.1	Seroprotection by TNA NF_{50} Antibody Levels Summary by Study Group	I, C	F, P, M
Table 14.2.1.2	Exploratory Seroprotection by TNA NF_{50} Antibody Levels Summary Comparisons	I, C	P, M
Table 14.2.1.3	TNA NF_{50} Antibody Levels Summary by Study Group	I, C	P, M
Table 14.2.1.4	Exploratory TNA NF_{50} Antibody Level Summary Comparisons	I, C	P, M
Table 14.2.1.5	Seroconversion by TNA NF_{50} Antibody Levels Summary by Study Group	I, C	P, M
Table 14.2.2.1	Seroconversion by TNA ED_{50} Antibody Levels Summary by Study Group	I, C	P, M
Table 14.2.2.2	TNA ED_{50} Antibody Levels Summary by Study Group	I, C	P, M

Table 14.2.3.1	Seroconversion by ELISA anti-PA IgG Antibody Levels Summary by Study Group	I, C	P, M
Table 14.2.3.2	ELISA anti-PA IgG Antibody Levels Summary by Study Group	I, C	P, M
Table 14.3.1.1.1	Summary of Adverse Events by Study Group	I, C	S
Table 14.3.1.1.2	Summary of Adverse Events for Dose 1 by Study Group	I, C	S
Table 14.3.1.1.3	Summary of Adverse Events for Dose 2 by Study Group	I, C	S
Table 14.3.1.1.4	Summary of Adverse Events for Dose 3 by Study Group	I, C	S
Table 14.3.1.1.5	Summary of Adverse Events by Study Group and Dose	I, C	S
Table 14.3.1.2.1	All Adverse Events by System Organ Class, Preferred Term and Study Group	I, C	S
Table 14.3.1.2.2	All Adverse Events by System Organ Class, Preferred Term and Study Group for Dose 1	I, C	S
Table 14.3.1.2.3	All Adverse Events by System Organ Class, Preferred Term and Study Group for Dose 2	I, C	S
Table 14.3.1.2.4	All Adverse Events by System Organ Class, Preferred Term and Study Group for Dose 3	I, C	S
Table 14.3.1.2.5	All Adverse Events by System Organ Class, Preferred Term, Study Group and Dose	I, C	S
Table 14.3.1.3.1	All Adverse Events by Type, Preferred Term and Study Group	I, C	S
Table 14.3.1.3.2	All Adverse Events by Type, Preferred Term and Study Group for Dose 1	I, C	S
Table 14.3.1.3.3	All Adverse Events by Type, Preferred Term and Study Group for Dose 2	I, C	S
Table 14.3.1.3.4	All Adverse Events by Type, Preferred Term and Study Group for Dose 3	I, C	S
Table 14.3.1.4.1	All Adverse Events by System Organ Class, Preferred Term, Maximum Severity and Study Group	I, C	S
Table 14.3.1.4.2	All Adverse Events by System Organ Class, Preferred Term, Maximum Severity and Study Group for Dose 1	I, C	S
Table 14.3.1.4.3	All Adverse Events by System Organ Class, Preferred Term, Maximum Severity Study Group for Dose 2	I, C	S
Table 14.3.1.4.4	All Adverse Events by System Organ Class, Preferred Term, Maximum Severity and Study Group for Dose 3	I, C	S

Table 14.3.1.5.1	All Adverse Events by System Organ Class, Preferred Term, Strongest Relationship to Investigational Product and Study Group	I, C	S
Table 14.3.1.5.2	All Adverse Events by System Organ Class, Preferred Term, Strongest Relationship to Investigational Product and Study Group for Dose 1	I, C	S
Table 14.3.1.5.3	All Adverse Events by System Organ Class, Preferred Term, Strongest Relationship to Investigational Product and Study Group for Dose 2	I, C	S
Table 14.3.1.5.4	All Adverse Events by System Organ Class, Preferred Term, Strongest Relationship to Investigational Product and Study Group for Dose 3	I, C	S
Table 14.3.1.6.1	All Adverse Events by System Organ Class, Preferred Term, Earliest Day of Onset and Study Group	I, C	S
Table 14.3.1.6.2	All Adverse Events by System Organ Class, Preferred Term, Earliest Day of Onset and Study Group for Dose 1	I, C	S
Table 14.3.1.6.3	All Adverse Events by System Organ Class, Preferred Term, Earliest Day of Onset and Study Group for Dose 2	I, C	S
Table 14.3.1.6.4	All Adverse Events by System Organ Class, Preferred Term, Earliest Day of Onset and Study Group for Dose 3	I, C	S
Table 14.3.1.7.1	Solicited Local Reactogenicity Symptoms by Maximum Severity and Study Group for Doses 1, 2 and 3	I, C	S
Table 14.3.1.7.2	Solicited Local Reactogenicity Symptoms by Maximum Severity and Study Group for Dose 1	I, C	S
Table 14.3.1.7.3	Solicited Local Reactogenicity Symptoms by Maximum Severity and Study Group for Dose 2	I, C	S
Table 14.3.1.7.4	Solicited Local Reactogenicity Symptoms by Maximum Severity and Study Group for Dose 3	I, C	S
Table 14.3.1.7.5	Solicited Local Reactogenicity Symptoms by Maximum Severity, Study Group and Dose	I, C	S
Table 14.3.1.8.1	Solicited Systemic Reactogenicity Symptoms by Maximum Severity and Study Group for Doses 1, 2 and 3	I, C	S

Table 14.3.1.8.2	Solicited Systemic Reactogenicity Symptoms by Maximum Severity and Study Group for Dose 1	I, C	S
Table 14.3.1.8.3	Solicited Systemic Reactogenicity Symptoms by Maximum Severity and Study Group for Dose 2	I, C	S
Table 14.3.1.8.4	Solicited Systemic Reactogenicity Symptoms by Maximum Severity and Study Group for Dose 3	I, C	S
Table 14.3.1.8.5	Solicited Systemic Reactogenicity Symptoms by Maximum Severity, Study Group and Dose	I, C	S
Table 14.3.1.8.6	Solicited Systemic Reactogenicity Symptoms by Strongest Relationship to Investigational Product and Study Group for Doses 1, 2 and 3	I, C	S
Table 14.3.1.8.7	Solicited Systemic Reactogenicity Symptoms by Strongest Relationship to Investigational Product and Study Group for Dose 1	I, C	S
Table 14.3.1.8.8	Solicited Systemic Reactogenicity Symptoms by Strongest Relationship to Investigational Product and Study Group for Dose 2	I, C	S
Table 14.3.1.8.9	Solicited Systemic Reactogenicity Symptoms by Strongest Relationship to Investigational Product and Study Group for Dose 3	I, C	S
Table 14.3.1.9.1	Unsolicited Adverse Events by System Organ Class, Preferred Term and Study Group	I, C	S
Table 14.3.1.9.2	Unsolicited Adverse Events by System Organ Class, Preferred Term and Study Group for Dose 1	I, C	S
Table 14.3.1.9.3	Unsolicited Adverse Events by System Organ Class, Preferred Term and Study Group for Dose 2	I, C	S
Table 14.3.1.9.4	Unsolicited Adverse Events by System Organ Class, Preferred Term and Study Group for Dose 3	I, C	S
Table 14.3.2.1.1	Serious Adverse Events by System Organ Class, Preferred Term and Study Group	I, C	S
Table 14.3.2.1.2	Medically Attended Adverse Events by System Organ Class, Preferred Term and Study Group	I, C	S
Table 14.3.2.1.3	Potentially Immune-Mediated Medical Conditions by System Organ Class, Preferred Term and Study Group	I, C	S
Table 14.3.2.1.4	All Adverse Events by System Organ Class, Preferred Term and Study Group Leading to Death	I, C	S

Table 14.3.2.2.1	All Adverse Events by System Organ Class, Preferred Term and Study Group Leading to Early Termination of Investigational Product	I, C	S
Table 14.3.2.2.2	All Adverse Events by System Organ Class, Preferred Term and Study Group Leading to Study Withdrawal	I, C	S
Table 14.3.3.1	Investigational Product Site Examination by Study Group for Dose 1	C	S
Table 14.3.3.2	Investigational Product Site Examination by Study Group for Dose 2	C	S
Table 14.3.3.3	Investigational Product Site Examination by Study Group for Dose 3	C	S
Table 14.3.4.1	Chemistry, Hematology and Urinalysis Clinical Laboratory Results by Study Group	C	S
Table 14.3.4.2	Shift from Baseline in Grading of Chemistry, Hematology and Urinalysis Clinical Laboratory Results by Study Group	C	S
Table 14.3.5.1	Vital Sign Parameters by Study Group	C	S
Table 14.3.5.2	Shift from Baseline in Grading of Vital Sign Parameters by Study Group	C	S

Note: Each table will be created once per applicable population. In addition, each table will be created once to show summaries by study group, and once to show summaries by pooled age or arm groups.

Listings

Listing Number	Listing Title	Applicable Reports (C=Final CSR)	Applicable Populations (NR=Not Randomized, R=Randomized, S=Safety, F=IFAP, P=IPPP M=MIPPP)
Listing 16.2.1.1	Disposition	C	R
Listing 16.2.1.2	Visit Completion	C	R
Listing 16.2.1.3	Analysis Populations	C	R
Listing 16.2.1.4	Reasons for Subject Ineligibility for Enrollment	C	NR
Listing 16.2.1.5	Reasons for Subject Ineligibility for 2nd Investigational Product Administration	C	S
Listing 16.2.1.6	Reasons for Subject Ineligibility for 3rd Investigational Product Administration	C	S
Listing 16.2.2.1	Protocol Deviations	C	R
Listing 16.2.4.1	Demographics and Baseline Physical Characteristics	C	S
Listing 16.2.4.2	Medical History	C	S
Listing 16.2.4.3	Immunization History	C	S
Listing 16.2.4.4	Prior and Concomitant Medications	C	S
Listing 16.2.4.5	Concomitant Immunizations	C	S
Listing 16.2.5	Investigational Product Administration Adherence	C	S
Listing 16.2.6	Serum TNA NF_{50}, TNA ED_{50} and ELISA anti-PA IgG Antibody Levels	C	F
Listing 16.2.7.1	Adverse Events	C	S
Listing 16.2.7.2	Serious Adverse Events	C	S
Listing 16.2.7.3	Medically Attended Adverse Events	C	S

Listing 16.2.7.4	Potentially Immune-Mediated Medical Conditions	C	S
Listing 16.2.7.5	Adverse Events Leading to Death	C	S
Listing 16.2.7.6	Potentially Life-Threatening (Grade 4) Adverse Events	C	S
Listing 16.2.7.7	Adverse Events Leading to Early Termination of Investigational Product	C	S
Listing 16.2.7.8	Adverse Leading to Study Withdrawal	C	S
Listing 16.2.7.9	Adverse Event Verbatim Text Coding List to Preferred Term	C	N/A
Listing 16.2.7.10	Investigational Product Site Examination	C	S
Listing 16.2.7.11	Participant-reported Diary Card Measurements of Investigational Product Site Erythema/Redness and Induration/Swelling	C	S
Listing 16.2.8.4	Chemistry, Hematology and Urinalysis Clinical Laboratory Results	C	S
Listing 16.2.9.1	Vital Signs	C	S
Listing 16.2.9.2	Electrocardiogram Results	C	S
Listing 16.2.9.3	High-Sensitivity C-Reactive Protein Assay Results for Subjects ≥66 Years	C	S
Listing 16.2.9.4	Screening HIV Antibody, Hepatitis B Surface Antigen and Hepatitis C Antibody Results	C	S
Listing 16.2.9.5	Screening Hemoglobin A1C Results	C	S
Listing 16.2.9.6	Screening Urine Drug Test Results	C	S
Listing 16.2.9.7	Autoantibody Assay Results	C	S
Listing 16.2.9.8	Urine Pregnancy Assessment	C	S
Listing 16.2.9.9	Pregnancies	C	S

Note: Additional listings may be produced based on actual study results.

Figures

Figure Number	Figure Title	Applicable Reports (I=Interim, C=Final CSR)	Applicable Populations (R=Randomized, S=Safety, F=IFAP, P=IPPP M=MIPPP)
Figure 14.2.1.1	TNA NF_{50} Antibody Levels Plot of Geometric Mean Levels and 95% CI Over Time	I, C	P, M
Figure 14.2.1.2	Seroprotection by TNA NF_{50} Antibody Levels at Visit 10 (Day 64)	I, C	F, P, M
Figure 14.2.1.3	TNA NF_{50} Antibody Levels Reverse Cumulative Distribution Plot at Visit 10 (Day 64)	I, C	P, M
Figure 14.2.2.1	TNA ED_{50} Antibody Levels Plot of Geometric Mean Levels and 95% CI Over Time	I, C	P, M
Figure 14.2.2.2	TNA ED_{50} Antibody Levels Reverse Cumulative Distribution Plot at Visit 10 (Day 64)	I, C	P, M
Figure 14.2.3.1	ELISA anti-PA IgG Antibody Levels Plot of Geometric Mean Levels and 95% CI Over Time	I, C	P, M
Figure 14.2.3.2	ELISA anti-PA IgG Antibody Levels Reverse Cumulative Distribution Plot at Visit 10 (Day 64)	I, C	P, M
Figure 14.2.4.1	TNA NF_{50} and ELISA anti-PA IgG Antibody Titer Scatter Plot at Visit 10 (Day 64)	C	P, M
Figure 14.2.4.2	TNA ED_{50} and ELISA anti-PA IgG Antibody Titer Scatter Plot at Visit 10 (Day 64)	C	P, M

Note: Each figure will be created once per applicable population. In addition, each figure will be created once to show data by study group, and once to show data by pooled age or arm groups.