STATISTICAL ANALYSIS PLAN

For

PROTOCOL NO.: GCAM_TET-01

A Clinical Study of the Safety and Antibody Responses of Plasma Donors Vaccinated with a Licensed Tdap Vaccine

Protocol Version No.: 3.0 Version Date: 25Jan2021

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Date: 08 November 2021

Prepared by: [redacted] Date: _____

Reviewed by: [redacted] Date: _____

Reviewed by: [redacted] Date: _____

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1. List of Abbreviations

Abbreviation	*Definition*
AE	Adverse event
CRF	Case report form
CSR	Clinical Study Report
ELISA	Enzyme-linked immunosorbent assay
I/E	Inclusion/Exclusion
HAV	Hepatitis A virus
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IU/mL	International Unit/ Mililiter
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
max	Maximum
min	Minimum
msec	Milliseconds
n	Number of observations
PI	Principal Investigator
PP	Per-protocol
QA	Quality Assurance
RPR	Rapid plasma reagin
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System, Organ, Class
SOP	Standard operating procedure
Tdap	Tetanus toxoid, diphtheria toxoid, acellular pertussis
US	United States
WHO	World Health Organization

2. Introduction

This analysis plan describes the core set of table summaries, data listings, graphic representations, and pre-planned statistical analyses to address the study objectives for protocol number GCAM-TET-01. In addition, *post hoc* exploratory analyses may also be performed to aid in interpretation of the data. Any prospective changes to the plan will be made, reviewed, and approved before the database is locked. Changes to the planned conduct of the analysis will be documented and justified in Clinical Study Report (CSR).

This SAP describes Safety evaluations, based on clinical parameters, laboratory testing and assessment of adverse events (AEs) etc., and efficacy evaluations based on anti-tetanus anitibody titers levels.

3. Protocol Summary

3.1. Study Objectives

Primary Objective

- To assess the safety of a licensed Tdap vaccine when given every 3 months for a total of 5 immunizations over a period of 12 months.

Secondary Objectives

- To assess anti-tetanus antibody titers over time of a licensed Tdap vaccine when given every 3 months for a total of 5 immunizations over a period of 12 months and for 6 months after the final immunization.

3.2. Study Design

This is a prospective, open label, single-arm, multi-center, Phase 2 study measuring the safety and tetanus antibody responses to Tdap vaccine administered to plasma donors every 3 months ±1 week for 12 months (5 vaccinations) with a 6 month follow-up after the last vaccination. After obtaining informed consent and screening for eligibility including plasmapheresis donor eligibility, subjects will have other baseline assessments performed and if eligible, will receive the scheduled vaccinations, will be assessed for adverse events (AEs) and have plasma samples collected with antibody titers reported each month thereafter for 11 months, and then at 1 and 6 months after the last vaccination. Subjects will undergo plasmapheresis prior to the second through the fifth vaccination and at the 1 month and 6 month post vaccination follow-up visits. As these subjects are participating in a standard donor plasmapheresis donor program, assessments for donor eligibility and routine plasmapheresis will be performed; however, only the data specifically required to meet the objectives of this study will be collected.

The study time and events schedule is shown in Table A. In addition to these study specific assessments routine screening procedures to assure plasma donor suitability was also performed. Some of the routine procedures performed as part of plasma donor screening evaluations such as vital signs, physical examinations, or laboratory tests were reported as AEs (if appropriate) on an AE eCRF.

3.3. Study Endpoints

Safety Endpoints:

- Incidence, severity, and relationship of AEs to the study vaccine in the time period between vaccinations and for the overall study period.

Efficacy endpoints:

- Anti-tetanus antibody titer levels after each vaccination presented at geometric means (GeoMean) over time.
- The numbers and percentages of subjects whose post vaccination antibody levels are <5 IU/mL; ≥5 IU/mL to 10 IU/mL; >10 IU/mL to 15 IU/mL; and >15 IU/mL after each vaccination.

Table A: Time and Events Schedule

Study Phase	**Screening**	**Visits (Month 0 to Month 12 ± 1 week)**												
Month	**-7 to -1 days**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit Number	**1**	**2/3**	**4**	**5**	**6/7**	**8**	**9**	**10/11**	**12**	**13**	**14/15**	**16**	**17**	**18/19**
Study Specific Procedures for which data are recorded on an eCRF														
Consent	X													
Eligibility checklist[a]	X	X			X			X			X			X
Demographics	X													
Medical history	X													
Medications	X	X			X			X			X			X
Vaccination		**1**			**2**			**3**			**4**			**5**
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma sample for anti-tetanus and anti-diphtheria antibody titer[b]	X		X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis/ serum creatinine[c]		X			X			X			X			X
Diary card review[d]		X	X	X	X	X	X	X	X	X	X	X	X	X
Procedures performed as part of routine plasma donor testing and pheresis														
Medical history[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infectious diseases[f]	X													
Immunization record	X													
Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pre-donation screening examination[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasmapheresis			Plasma donations may occur 2-times per week with at least one-calendar day between donations.											

[a]At screening, the reasons a subject is not eligible for the study (screen failure) will be captured on a Reasons Not Eligible eCRF. Subjects will be checked to ensure that they meet study eligibility criteria prior to each vaccination. If not eligible, a Reasons not Eligible for Vaccination eCRF will be completed.
[b]Tetanus and diphtheria antibody test samples will be collected, frozen and tested at a later date. Samples are collected from plasma donations performed at these visits. If a plasmapheresis was not scheduled or performed at this visit (± 1 week) then a blood sample collected for plasma separation may be used instead.
[c]Serum creatinine and urinalysis - measured 1-3 days after each study vaccination. If the subject does not return to the center within this time frame, the sample should be collected and tested at the next visit to the center.
[d]The subject's diary card will be reviewed at each monthly visit for recording of AEs and medications.
[e]Medical history is updated at all visits after the screening visit including reports of pregnancy by female participants.
[f]Anti-HIV-1/2, HBsAg, Anti-HCV, SPE/RPR, Indirect Coombs, and PCR testing for HIV-1, HBV and HCV, HAV, Parvovirus B19 are tested from plasma samples collected from two sequential plasma donations and must be negative for a subject to be eligible for the study. Infectious disease testing is also performed on plasma samples collected from plasma donations and if a subject is positive for any of these infectious diseases, they will be taken off study. In addition, RPR (syphilis test) is performed every 4 months.
[g]Pre-donation screening assessments include a full physical exam performed annually, vital signs and hematocrit and total protein at each donation. If the subject is already a donor of record, the full physical examination will only be performed when regularly scheduled

Table A Continued: Time and Events Schedule

	Follow-Up 1	**Follow-Up 2**
Month	**13**	**18**
Visit Number	**20**	**21**
Medications	X	X
AEs	X	X
Plasma sample for anti-tetanus and anti-diphtheria antibody titer	X	X
Diary card review	X	X
Subject disposition		X
Medical history	X	X
Body weight	X	X
Medications	X	X
Pre-donation screening examination	X	X
Subject Disposition[a]		X

[a] The final disposition of the subject will be reported on a Subject Disposition eCRF including if the subject completed the full study or withdrew early and the reason for early withdrawal. This eCRF will be completed at an earlier visit if the subject withdrew from the study.

4. Definition of Analysis Sets

Intention-to-treat (ITT) Population: The ITT population will consist of all subjects who are enrolled into the study and received any amount of investigational product. This population will be used in safety analysis.

Per-protocol (PP) Population: The per-protocol population will consist of all subjects in the ITT population who received all 5 TdaP vaccinations and completed the 6 month follow-up visit after the final vaccination.

5. Assessments and Justification of Study Endpoints

The schedule of Assessments for the study is shown in **Table A**.

5.1. Safety Endpoints

Adverse Events: AEs will include any treatment emergent unfavorable and unintended sign or symptom inlcuding abnormal laboratory findings that occur at any time after the subject has signed informed consent until the second follow up visit after the last study vaccination, whether or not considered drug related.

Severity: All AEs will be assessed for severity by the investigator. Assignment of grade based on the intensity of symptoms and the degree of limitation of usual daily activities will be done according to severity using the following criteria:

Mild: The AE did not cause interference with the subject's activity.

Moderate: The AE produced limited functional impairment and may have required therapeutic intervention. The AE produced no sequelae.

Severe: The AE resulted in significant impairment of function and may have lead to temporary inability to resume the subject's normal life pattern.

Relationship: The degree of certainty for which the AE/SAE is attributed to the investigational product or alternative causes will be determined by the investigator's use of clinical judgment in conjunction with the assessment of a plausible biologic mechanism, a temporal relationship between the onset of the event in relation to receipt of the investigational product, and identification of possible alternate etiologies including underlying disease, concurrent illness or concomitant medications. Only a physician can make this determination.

The following drug relationships will be used for this clinical study:

Unrelated: There is no temporal relationship between the event and the administration of the product or the event is clearly due to the subject's medical condition, other therapies, or accident.

Unlikely: There is evidence of exposure to the product but there is another more likely cause of the event.

Possible: There is some temporal relationship between the event and the administration of the product and the event is unlikely to be explained by the subject's medical condition or other therapies.

Probable: The temporal relationship between the event and the administration of the product is compelling, and the subject's medical condition and other therapies cannot explain the event.

Definite: The event follows a reasonable temporal sequence from administration of the medication or follows a known or suspected response pattern to the medication.

The categories of definite, probable, and possible will be considered investigational product related with regards to summary statistics.

AE Actions and Outcomes: For each AE that is reported the actions taken with respect to study drug including: 1) none, 2) study drug discontinued, or 3) study drug interrupted will be recorded on the AE CRF. Also, outcomes will also be recorded including: 1) Fatal; 2) Resolved without sequelae; 3) Resolved with sequelae; 4) Ongoing, and 5) Unknown. If the AE required any treatment, this will also be recorded.

Serious Adverse Events (SAE): An AE or suspected adverse reaction is considered "serious" if, in the view of either the PI or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is an important medical event that may not result in death, be life threatening, or require hospitalization, but based on appropriate medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Solicited Adverse Events: Solicited AEs will be those AEs that occur for up to 3 days after each vaccination. The severity rating scale in Table B will be provided to the subject, to assess the severity of solicited AEs recorded in the diary. At the diary review, if any items are checked, a clinician will review these with the subject to confirm that the appropriate severity rating was selected.

Table B: Severity Rating Scale for Solicited Adverse Events

Adverse Event	Grade 0	Grade 1	Grade 2	Grade 3
Injection site redness	None	2.5 – 5 cm	5.1 – 10 cm	> 10 cm
Urticaria or other rash	None	No interference with activity	Some interference with activity	Significant; prevents daily activity
Injection site tenderness/ pain	None	No interference with activity	Some interference with activity	Significant; prevents daily activity

Adverse Event	Grade 0	Grade 1	Grade 2	Grade 3
Injection site swelling	None	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity
Fever	None	100.4 – 101.1	101.2 – 102.0	102.1 – 104
Headache	None	No interference with activity	Repeated use of nonnarcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity
Nausea/vomiting	None	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration
Chills, fatigue, joint pain malaise, muscle weakness (myalgia)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity

5.2. Efficacy Endpoints

When plasmapheresis is scheduled during one of the clinical protocol monthly study visits, a sample of the plasma collected during plasmapheresis will be collected. Samples will be stored at ≤ -20°C until tested and will be tested throughout the study shortly after collection. Tetanus antibody responses will be measured at a central laboratory using an enzyme-linked immunosorbent assay (ELISA) [VaccZyme Tetanus Toxoid IgG – Binding Site] and expressed as international units per mL (IU/mL).

5.3. Baseline and Other Assessments

A complete medical history and demography (gender, age, race, and ethnicity) will be collected at the screening visit. Medications being taken by the subject in the 7-day period prior to the first vaccination through the completion of the study along with complete immunization history will be recorded and reported on an eCRF.

Vitals signs, full physical examinations and hematocrit and total protein determinations as part of the routine plasmapheresis will be assessed during pre-donation screening.

Infectious disease testing will be performed on all plasma samples collected from plasma donations and if a subject is positive for any of these infectious diseases, they will be taken off study. In addition, RPR (syphilis test) is performed every 4 months. If the subject is a first time donor, they must have two sequential plasma donations that are negative for the following infectious diseases to be eligible for plasmapheresis: Anti-HIV-1/2, HBsAg, Anti-HCV, SPE/RPR, Indirect Coombs, and PCR testing for HIV-1, HBV and HCV, HAV, and Parvovirus B19.

An eligibility checklist will be completed at screening. If the subject is not eligible for the study, a Reasons Not Eligible eCRF will be completed.

A dipstick urinalysis will be performed that tests for protein, blood, leukocyte esterase, nitrates, pH, specific gravity, ketones, bilirubin, and glucose. A blood sample will also be collected for a serum creatinine test. These tests will be performed to monitor for the possible development of immune complex-mediated glomerular disease.

Anti-diphtheria antibody levels will be measured at a central laboratory using the EUROIMMUN Anti-Diphtheria Toxoid ELISA (IgG). High anti-diphtheria titers will be assessed for an association with an increase in reactogenicity.

6. Hypotheses to be Tested

Hypothesis tests will be performed in order to determine if there is an association between reactogenicity and anti-diphtheria titers. Null Hypothesis of no association between reactogenicity and anti-diphtheria titers will be tested on Slope obtained using simple linear regression analysis at alpha=0.01 using two-sided tests.

7. Sample Size

One hundred subjects will be enrolled in this study.

8. Data Quality Assurance

Data quality is maintained by ensuring accuracy of data, reviewing protocol prior to study start, auditing data acoording to GCP and periodic site monitoring by sponsor's designees. Written instructions will be provided for collection, preparation, and shipment of blood spot samples.

The Sponsor's designees will review source documents for accuracy and completeness during on-site and remote monitoring visits and any discrepancies will be resolved with the PI, as appropriate.

Significant and/or repeated noncompliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in study site termination and regulatory authority notification.

9. Statistical Considerations

9.1. General Considerations

Descriptive statistics will be used to present study data. Continuous variables will be presented as number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max) values. Categorical and dichotomous variables will be presented as counts and percentages. As it is expected that titers will not be normally distributed, geometric means (GeoMean) will be used to summarize anti-tetanus and anti-diphtheria antibody titers. All data will be presented in listings.

Analyses will be done using SAS v9.4.

9.2. Participant Accountability and Protocol Deviations

The disposition of all study subjects will be summarized including the total numbers screened, eligible, enrolled, ITT, per-protocol, withdrawn, and completed. Accountability data including study termination and reason will be provided in a summary table and listing for all subjects who were enrolled. A listing of all protocol deviations will be provided.

9.3. Demographics, Pre-donation Screening and Treatment Compliance

Subject demographics which includs age (years), gender, ethnicity and race will be summarized for the ITT and Per-protocol population. Pre-donation screening for plasmapheresis check includes full physical examinations, vital signs, total proteins and hematocrit at each donation, will be summarized by visit and listed by subject and visit. Compliance with scheduled vaccinations will also be summarized, including number of doses and total dose of investigational product. Protocol compliance will be presented as percentages of subjects attending scheduled visits over the duration of the study.

9.4. Immunizations, Prior and Concomitant Medications

Prior and comcomitant medications will be listed by subject. Medications and treatments with an end date prior to the first dose of study drug will be considered prior medications and will be noted in listing. If the date is partial or unknown, then medication will be considered as concomitant. Any prior immunizations will be listed by subject.

9.5. Analysis of Safety Endpoints

Treatment emergence will be evaluated for all AEs. Treatment-emergent adverse events (TEAEs) are those that occur on or after the same date and time of first dose of study drug. TEAEs will be coded using the most recent version of the Medical Dictionary of Regulatory Affairs (MedDRA) by assigning a preferred term and will be grouped by system, organ, and class (SOC) designation. AEs occurring after each vaccination up to the time of the next vaccination and separately over the whole study period will be summarized. Separate tables will be provided for solicited AEs reported within the 3 day period after each vaccination.

Each AE will be counted once only by preferred term for a given study subject within each post vaccination time period prior to the next vaccination or up to the 6-month follow-up visit after the last vaccination. If the same AE occurred on multiple occasions, the highest severity and relationship to investigational product will be assumed within each time period.

The summary tables will include an overall summary of number and percentage of subjects reporting each TEAE, summary by relationship, summary by severity will be presented by each vaccination period and overall.

Listings of each individual AE including start date, stop date, severity, relationship, duration, outcome, and actions taken will be provided.

Reactogenicity is defined as the total count of a set of solicited AEs that are expected after a vaccine. A regression analysis will be performed with reactogenicity as the dependent variable and anti-diphtheria titers as the independent variable to determine if there is an association. Anti-diptheria titer is not expected to be normally distributed and will be natural log transformed. Null Hypothesis of no association between reactogenicity and anti-diphtheria titers will be tested on

Slope obtained using simple linear regression analysis at alpha=0.01 using two-sided tests. The null hypothesis states that the slope is equal to zero, and the alternative hypothesis states that the slope is not equal to zero. No adjustment for covaiates will be made. The following SAS procedure PROC REG may be used.

Proc reg data=data;
Model reactogenicity =log(anti_diptheria_titers);
Run;

In addition, 2x2 tables will be created with presence or absence of moderate to severe reactogenicity versus high or not anti-diphtheria titers. Cut points of 75th percentile or 90th percentile of the anti-diphtheria titers will be used to define high level. The following SAS procedure PROC FREQ may be used.

Proc freq data=data;
*Table reactogenicity*anti_diptheria_titers/ nopercent nocol;*
Weight count;
Run;

9.6. Clinical Laboratory Data

Laboratory data for urinalysis results and serum creatinine levels will be presented as summary statistics by visit as well as in by-subject data listings. The number and percentage of subjects with serum creatinine > 1.5 x upper limit of normal and urine indicative for proteinuria (2+) or hematuria (blood ≥ 50 erythrocytes/µL).

9.7. Analysis of Efficacy Endpoints

Tetanus antibody titers (IU/mL) will be presented as geometric mean (GeoMean), minimum and maximum concentrations after each vaccination at all collection time points. Linear plots of the geometric mean ± Standard errors of Tetanus antibody titers will be provided by each collection time points.

The numbers and percentages of subjects whose post vaccination anti-tetanus antibody levels are <5 IU/mL; ≥5 IU/mL to 10 IU/mL; >10 IU/mL to 15 IU/mL; and, >15 IU/mL will be presented in a table over time. The percentages of subjects in each of these categories will also be presented in scatter plot over collection time.

10. Handling of Missing Data and Missing Date

Missing Data will not be imputed.

Missing dates are handled as follows:

- Missing day: The first day of the month will be used.
- Missing Month: The first month of the year will be used.
- Completely missing dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

11. Validation of Programming Code

All SAS code used to generate tables, listings, and figures will be validated and reviewed before being finalized. The validation process will be used to determine that the numbers are produced by a statistically valid method and that the execution of the computations is correct. Qualified personnel who have not previously been involved in the production of the original programming code will perform the validation procedures. Methods of validation include independent programming and comparison to data listings. Tables will be reviewed for accuracy, consistency with this plan, consistency within tables, and consistency with corresponding output. Once validation is complete, a quality control reviewer will perform a final review of the documents for accuracy and consistency. Upon completion of validation and quality review procedures, all documentation will be collected and filed in the study documentation files at Fast-Track.

12. Changes to Planned Analyses

There are no changes between protocol-defined statistical analyses and those presented in this SAP.

13. Appendix A: Table and Figure Shells

List of Tables and Figures

Table 1: Summary of Subject Disposition - All Consented Subjects

Disposition Category	Total
Total Consented	xx
Total Eligible	xx
Enrolled and Received First Vaccination	xx
Data below is n (%) of enrolled	
Intention-to-treat (ITT) Population	xx (x.x)
Per-protocol (PP) Population	xx (x.x)
Subjects completing study (Completed Month 18 visit)	xx (x.x)
Subjects terminating early[a]	
AE or SAE	xx (x.x)
Protocol violation	xx (x.x)
Subject did not comply with protocol	xx (x.x)
Continued participation will pose a risk to the subject	xx (x.x)
Pregnancy	xx (x.x)
Subject withdrew participation	xx (x.x)
Subject no longer eligible for study participation	xx (x.x)
Other	xx (x.x)

[a]Subjects may have been terminated for more than one reason, thus numbers will not add up to the total numbers of subjects.

<Program Name: Time and Date>

Table 2: Reasons for Not Meeting Eligibility Criterion - Not Enrolled Subjects

Reason	n= xx
Informed consent Withdrawn	xx (x.x%)
(List all reasons)	xx (x.x%)

<Program Name: Time and Date>

Table 3: Demographics and Subject Characteristics

Characteristic	ITT N=xx	Per-protocol N=xx
Gender		
Male	xx (x.x%)	xx (x.x%)
Female	xx (x.x%)	xx (x.x%)
Age (years at date of consent)		
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x
Min-Max	(xx – xx)	(xx – xx)
Maximum		
Race		
Black or African American	xx (x.x%)	xx (x.x%)
American Indian or Alaskan Native	xx (x.x%)	xx (x.x%)
Asian	xx (x.x%)	xx (x.x%)
Native Hawaiian or Other Pacific Islander	xx (x.x%)	xx (x.x%)
White	xx (x.x%)	xx (x.x%)
OtherUnknown	xx (x.x%)	xx (x.x%)
	xx (x.x%)	xx (x.x%)
Ethnicity		
Hispanic or Latino	xx (x.x%)	xx (x.x%)
Not Hispanic or Latino	xx (x.x%)	xx (x.x%)
Not Reported	xx (x.x%)	xx (x.x%)

<Program Name: Time and Date>

Table 4: Summary of Protocol and Treatment Compliance

	ITT N=xx
Protocol compliance rate[a]	
Month 0	xx.x%
Month 3	xx.x%
Month 6	xx.x%
Month 9	xx.x%
Month 12	xx.x%
Number of Tdap vaccinations	
Mean (SD)	xx.x (x.xx)
Median	xx.x
Min-Max	(xx – xx)
Total Tdap vaccination dose (mL)	
Mean (SD)	xx.x (x.xx)
Median	xx.x
Min-Max	(xx – xx)

[a]Protocol compliance is presented as percentages of subjects attending each scheduled treatment visit.

<*Program Name: Time and Date*>

Table 5: Summary of Plasmapheresis Check by Visit - ITT Population

Visit		n (%)
Screening	Eligible for Plasmapheresis	
	Yes	xx.x (x.xx)
	No, Temporary	xx.x (x.xx)
	No, Permanent	xx.x (x.xx)
	If "No, Temporary", Inclusion Criteria not Met	
	Temperature: 97.0 - 99.5 °F	xx.x (x.xx)
	Blood Pressure: 90 - 180/50 – 90 mmHg	xx.x (x.xx)
	Pulse: 50 - 100 beats/min	xx.x (x.xx)
	(List all criteria not met)	
(Repeat for all visits)		

<Program Name: Time and Date>

Table 6: Summary of Treatment-emergent Adverse Events - ITT Population

	Vaccination Number					
	1 N=xx	**2 N=xx**	**3 N=xx**	**4 N=xx**	**5 N=xx**	**Overall N=xx**
Number of AEs	xx	xx	xx	xx	xx	xx
Number of SAEs	xx	xx	xx	xx	xx	xx
Number of AEs related to study product	xx	xx	xx	xx	xx	xx
Number (%) of subjects with						
At least one AE	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
At least one SAE	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
At least one AE related to study product	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
Number of AEs by severity						
Mild	xx	xx	xx	xx	xx	xx
Moderate	xx	xx	xx	xx	xx	xx
Severe	xx	xx	xx	xx	xx	xx
Number of AEs by relationship to study product	xx	xx	xx	xx	xx	xx
Unrelated	xx	xx	xx	xx	xx	xx
Unlikely	xx	xx	xx	xx	xx	xx
Possible	xx	xx	xx	xx	xx	xx
Probable	xx	xx	xx	xx	xx	xx
Definite						
Serious?	xx	xx	xx	xx	xx	xx
Yes	xx	xx	xx	xx	xx	xx
No						

Note: AEs occurring after each vaccination up to the time of the next vaccination is summarized.

<Program Name: Time and Date>

Table 7: Summary of Solicited Treatment-emergent Adverse Events - ITT Population

	Vaccination Number					
	1 N=xx	**2 N=xx**	**3 N=xx**	**4 N=xx**	**5 N=xx**	**Overall N=xx**
Number of Solicited TEAEs	xx	xx	xx	xx	xx	xx
Number of AEs related to study product	xx	xx	xx	xx	xx	xx
Number (%) of subjects with						
At least one soliciated TEAE	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
At least one AE related to study product	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
Number of Solicited TEAEs by severity						
Mild	xx	xx	xx	xx	xx	xx
Moderate	xx	xx	xx	xx	xx	xx
Severe	xx	xx	xx	xx	xx	xx
Number of Solicited TEAEs by relationship to study product	xx	xx	xx	xx	xx	xx
Unrelated	xx	xx	xx	xx	xx	xx
Unlikely	xx	xx	xx	xx	xx	xx
Possible	xx	xx	xx	xx	xx	xx
Probable	xx	xx	xx	xx	xx	xx
Definite						

N = Number of Subjects

Note: Solicited AEs reported within the 3 day period after each vaccination is summarized.

<Program Name: Time and Date>

Table 8: Number (%) of Subjects with Treatment-emergent Adverse Events by System Organ Class and Preferred Term - ITT Population

	Vaccination Number					
System, Organ, Class/ Preferred Term	**1 N=xx n (%)**	**2 N=xx n (%)**	**3 N=xx n (%)**	**4 N=xx n (%)**	**5 N=xx n (%)**	**Overall N=xx n (%)**
SOC 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Subjects are counted only once within each system organ class and preferred term.

<Program Name: Time and Date>

Table 9: Number (%) of Subjects withSolicited Treatment-emergent Adverse Events by System Organ Class and Preferred Term - ITT Population

	Vaccination Number					
System, Organ, Class/ Preferred Term	**1 N=xx n (%)**	**2 N=xx n (%)**	**3 N=xx n (%)**	**4 N=xx n (%)**	**5 N=xx n (%)**	**Overall N=xx n (%)**
SOC 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

: Note: Solicited AEs reported within the 3 day period after each vaccination is summarized.

Subjects are counted only once within each system organ class and preferred term.

<Program Name: Time and Date>

Table 10: Summary of Subjects with Treatment-emergent Adverse Events by Severity and Relationship - ITT Population

System, Organ, Class\ Preferred Term	Number of Subjects (%) (N=xx)								
	Mild		Moderate		Severe		All Grades		Total
	R	NR	R	NR	R	NR	R	NR	R + NR
SOC									
Preferred Term	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Subjects are counted only once by preferred term at the highest severity grade and closest relationship to the investigational product.
R= Related to investigational product (possible, probable, definite). NR = Not related to investigational product (unrelated, unlikely).

Table 11: Contingency Table of Reactogenicity and Anti-diptheria titers - ITT Population

Vaccination Number	Moderate to Severe Reactogenicity	Anti-diptheria Titers		Total
		High = Yes	High = No	
		n (%)	n (%)	n (%)
1	**Present**	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Absent	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	**Present**	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Absent	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	**Present**	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Absent	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	**Present**	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Absent	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)
5	**Present**	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Absent	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)
Overall	**Present**	xx (xx.x)	xx (xx.x)	
	Absent	xx (xx.x)	xx (xx.x)	
	Total	xx (xx.x)	xx (xx.x)	

Note: Reactogenicity is defined as the total count of a set of solicited AEs that are expected for up to 3 days after each vaccination. Cut points of 75th percentile of the anti-diphtheria titers is used to define high level.
<Program Name: Time and Date>

Table 12: Summary of Serum Creatinine and Urinalysis Tests - ITT Population

Parameter (Unit)		Month 0 n (%)	Month 3 n (%)	Month 6 n (%)	Month 9 n (%)	Month 12 n (%)
Serum Creatinine	Low	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	High	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Specific Gravity	1.000	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	1.005	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	…….	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
pH	**5**	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	6	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	….	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Leucocytes	Negative	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	Trace	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	……	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Nitrite	Negative	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	Positive	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Protein (mg/dL)	Negative	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	Trace	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	…..	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Glucose (mg/dL)	Normal	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	50	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	…….	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Ketones	Negative	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	+/small	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	……	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Urobilinogen	Normal	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	1	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	…..	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Bilirubin	Negative	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	+	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	……..	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Blood/Hemoglobin (ery/uL)	Negative	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	Trace(blood)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	…….	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)

Table 13: Summary of Anti-tetanus Antibody Titers (IU/mL)

Visit	Statistics	ITT (N=xx)	Per-protocol (N=xx)
Screening	n	xx	xx
	Geometric Mean (SD)	xx.x (x.xx)	xx.x (x.xx)
	Min-Max	(xx.x-xx.x)	(xx.x-xx.x)
	n		
	Geometric Mean (SD)	xx	
Month 1	Minimum	xx.x (x.xx)	xx
	Maximum	xx.x	xx.x (x.xx)
		xx.x	xx.x
			xx.x
(Repeat for all visits)			

<Program Name: Time and Date>

Table 14: Summary of Anti-diphtheria Antibody Titers (IU/mL)

Visit	Statistics	ITT (N=xx)	Per-protocol (N=xx)
Screening	n	xx	xx
	Geometric Mean (SD)	xx.x (x.xx)	xx.x (x.xx)
	Min-Max	(xx.x-xx.x)	(xx.x-xx.x)
	n	xx	xx
Month 1	Geometric Mean (SD)	xx.x (x.xx)	xx.x (x.xx)
	Min-Max	(xx.x-xx.x)	(xx.x-xx.x)
(Repeat for all visits)			

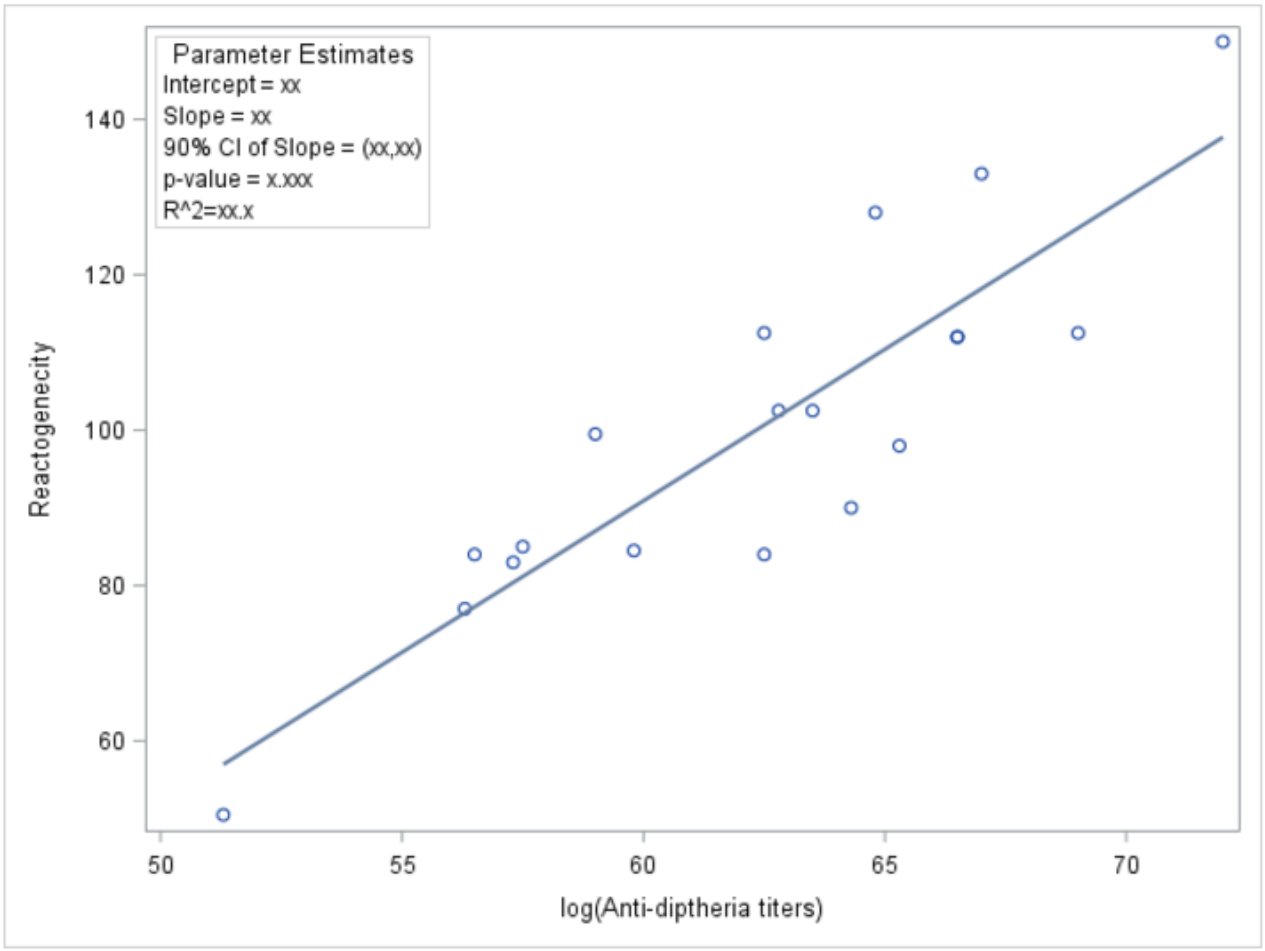
<Program Name: Time and Date>

Table 15: Number (%) of Subjects with Post Vaccination Anti-tetanus Antibody Levels

Visit	Anti-tetanus Antibody Levels	ITT (N=xx)	Per-protocol (N=xx)
Screening	< 5 IU/mL	xx.x (x.xx)	xx.x (x.xx)
	≥ 5 to 10 IU/mL	xx.x (x.xx)	xx.x (x.xx)
	≥10 to 15 IU/mL	xx.x (x.xx)	xx.x (x.xx)
	≥ 15 IU/mL	xx.x (x.xx)	xx.x (x.xx)
Month 1	< 5 IU/mL	xx.x (x.xx)	xx.x (x.xx)
	≥ 5 to 10 IU/mL	xx.x (x.xx)	xx.x (x.xx)
	≥ 10 to 15 IU/mL	xx.x (x.xx)	xx.x (x.xx)
	≥ 15 IU/mL	xx.x (x.xx)	xx.x (x.xx)
(Repeat for all visits)			

<Program Name: Time and Date>

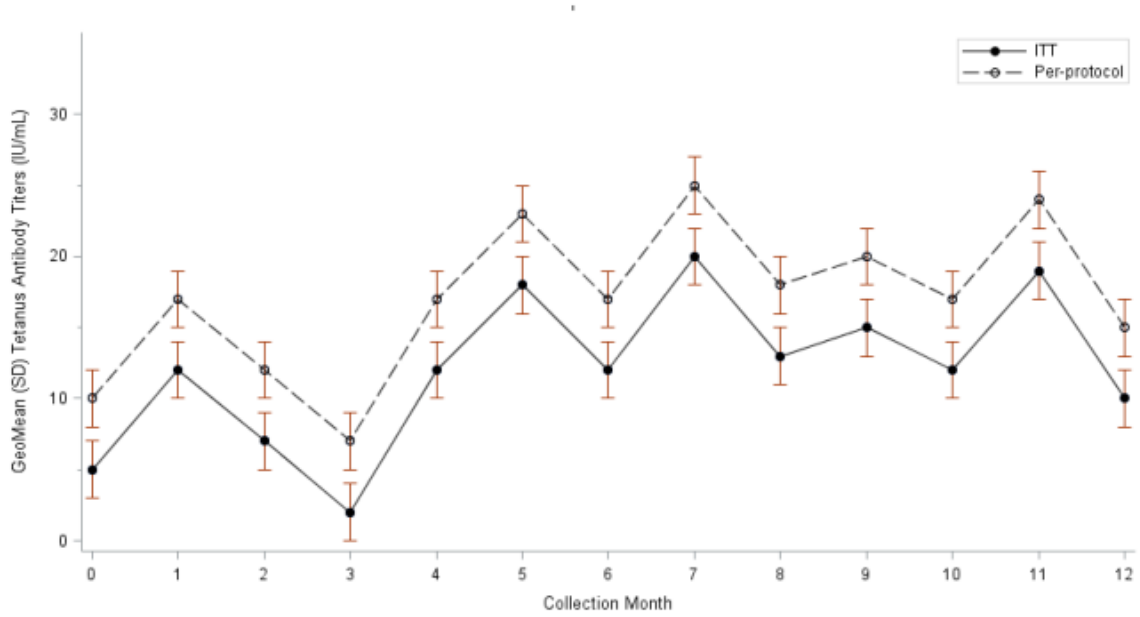
Figure 1: Regression Plot of Reactogenicity versus Anti-diptheria titers - ITT Population



Note: Reactogenicity is defined as the total count of a set of solicited AEs that are expected for up to 3 days after each vaccination.

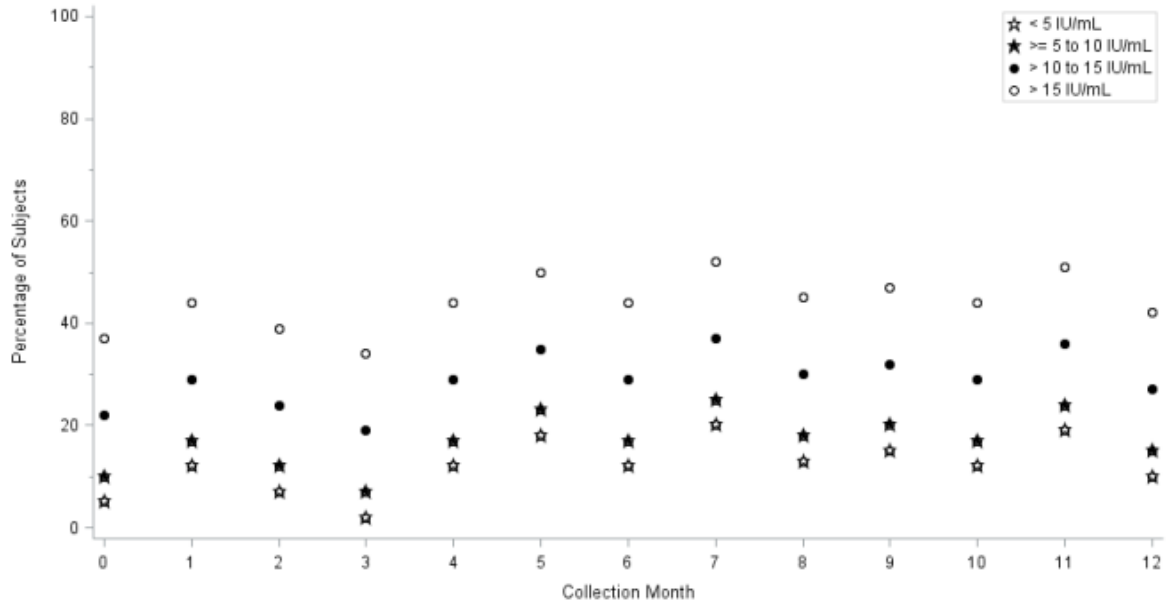
<Program Name: Time and Date>

Figure 2: Plot of GeoMean (± SD) of Tetanus Antibody Titers



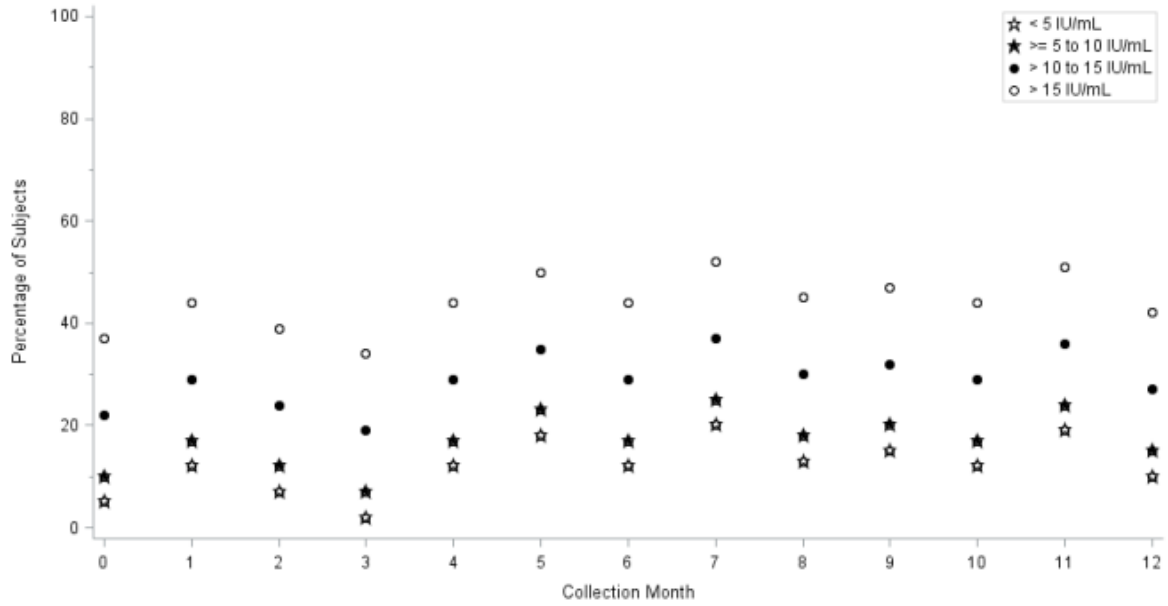
<Program Name: Time and Date>

Figure 3: Scatter Plot of Percentage of Subjects with Post Vaccination Anti-tetanus Antibody Levels – ITT Population



<Program Name: Time and Date>

Figure 4: Scatter Plot of Percentage of Subjects with Post Vaccination Anti-tetanus Antibody Levels – Per-protocol Population



<Program Name: Time and Date>

14. Appendix B: Listing Shells

Listing 1: Subject Disposition –Enrolled Subjects

Subject Number	Consent to Study Date	ITT Subject	Per-protocol Subject	Date of Last Visit/Contact	Study Completed?	Reasons for Early Discontinuation	Reason Detail
xxxx	ddmmmyyyy	Y/N	Y/N	ddmmmyyyy	Y/N	xxxxxxxx	xxxx

Programming Note: Subject ID.
<Program Name: Time and Date>

Listing 2: Reasons for Not Meeting Eligibility Criteria – All Subjects

Subject Number	Reason for Screen Failure	Other Description
xxxx	Subject withdrew consent	
	(list all reasons)	
	Other:	Verbatim text

Programming Note: sorted by Subject number.
<Program Name: Time and Date>

Listing 3: Protocol Deviations – All Subjects

Subject Number	Deviation Date	Deviation Detail
xxxx	dd/mmm/yyyy	Verbatim text

Note: Only subjects with protocol deviations are listed.
Programming Note: Sorted by Subject number.
<Program Name: Time and Date>

Listing 4: Demographics and Subject Characteristics– ITT Population

Subject Number.	Age at Date of Consent (Years)	Gender	Race	Ethnicity
xxxx	xx	Male	White	Hispanic or Latino
		Female	Other	Not Hispanic of Latino
				Not Recorded

Programming Note: Sorted by subject number. Insert verbatim when "Other" race is selected.
<Program Name: Time and Date>

Listing 5: Baseline Medical History – ITT Population

Subject Number	History Verbatim Term	Start Date	Stop Date	Start Day (relative to start of treatment)	Stop Day (relative to start of treatment)	Ongoing?
xxxx	xxxx	dd/mmm/yyyy	dd/mmm/yyyy	xxx	xxx	Y/N

<Program Name: Time and Date>

Listing 6: Plasmapheresis Check – ITT Population

Subject Number	Visit	Date of Plasmapheresis Check	Eligible for Plasmapheresis	Inclusion Criteria Not Met
xxxx		dd/mmm/yyyy	Yes	Xxxxxxx

<Program Name: Time and Date>

Listing 7: Previous Immunizations – ITT Population

Subject Number	Date of Previous Immunization	Type of Previous Immunization
xxxx	dd/mmm/yyyy	

Programming Note: Sorted by subject number, exam date.
<Program Name: Time and Date>

Listing 8: Tdap Vaccination – ITT Population

Subject Number	Date of Tdap Vaccination	Visit	Tdap NDC Number	Tdap Lot Number	Problems with the injection?	Specify
xxxx	dd/mmm/yyyy	Month 0			Y/N	Verbatim text

Programming Note: Sorted by subject number, exam date.
<Program Name: Time and Date>

Listing 9: Serum Creatinine and Urinalysis Tests Results – ITT Population

Subject Number	Date of Collection	Visit	Test Name (Unit)	Result	Reason not Collected
xxxx	dd/mmm/yyyy	Screening	Creatinine (Unit)	Xxx	Xxx
		(all Visits)	Glucose	Xxx	Xxx/xx

Programming Note: Sorted by subject number, Exam Date .
<Program Name: Time and Date>

Listing 10: Anti-tetanus and Anti-diptheria Antibody Tests Results – ITT Population

Subject Number	Date of Collection	Visit	Plasma Sample Identification #	Test Name (Unit)	Result	Reason not Collected, Specify
xxxx	dd/mmm/yyyy	Screening		xxx	Xxx	Xxx
		(all Visits)		xxx/xx	Xxx/xx	Xxx/xx
		Unscheduled				

Programming Note: Sorted by subject number, Exam Date.
<Program Name: Time and Date>

Listing 11: Adverse Events – ITT Population

Subject Number	AE Name/ MedDRA PT[a]/ SOC[b]	Onset Date/ Stop Date	Onset Day/ Duration (Days)	Severity	TEAE/ Vaccine Number	Serious? /SAE Description	Outcome	Relationship to Study Product/ Action Taken	Other Actions, Specify
xxxx	xxxx/ xxxx / xxxx	dd/mmm/yyyy dd/mmm/yyyy or Ongoing	Xx/xx	Mild Moderate Severe		Y/Xxx N	Resolved Resolved with sequelae	Unrelated Unlikely Possible Probable	

[a] PT=Preferred Term; [b] SOC=System, Organ, and Class
Programming Note: Sorted by Subject Number, Onset Date.
<Program Name: Time and Date>

Listing 12: Solicited Adverse Events – ITT Population

Subject Number	Vaccination Number	AE Name/ MedDRA PT[a]/ SOC[b]	Onset Date/ Stop Date	Onset Day/ Duration (Days)	Severity	TEAE/ Vaccine Number	Serious?	Outcome	Relationship to Study Product/ Action Taken
xxxx	1 2	xxxx/ xxxx / xxxx	dd/mmm/yyyy dd/mmm/yyyy or Ongoing	Xx/xx	Mild Moderate Severe		Y N	Resolved Resolved with sequelae	Unrelated Unlikely Possible Probable

[a] PT=Preferred Term; [b] SOC=System, Organ, and Class
Note: Solicited AEs reported within the 3 day period after each vaccination is listed.
Programming Note: Sorted by Subject Number, Onset Date.
<Program Name: Time and Date>

Listing 13: Adverse Events Leading to Withdrawal – ITT Population

Subject Number	AE Name/ MedDRA PT[a]/ SOC[b]	Onset Date/ Stop Date	Onset Day/ Duration (Days)	Severity	TEAE/ Vaccine Number	Serious?	Outcome	Relationship to Study Product/ Action Taken	Other Actions, Specify
xxxx	xxxx/ xxxx / xxxx	dd/mmm/yyyy dd/mmm/yyyy or Ongoing	Xx/xx	Mild Moderate Severe		Y/Xxx N	Resolved Resolved with sequelae	Unrelated Unlikely Possible Probable	

[a] PT=Preferred Term
[b] SOC=System, Organ, and Class
Programming Note: Sorted by Subject Number, Onset Date.
<Program Name: Time and Date>

Listing 14: Serious Adverse Events – ITT Population

Subject Number	Age (Years) at Screening	Gender	SAE Name	SAE Description	Considered serious because	Onset Date/ Stop Date	Vaccination Number	Death Date
xxxx	xx	Male Female	Verbatim text	Verbatim text	Death Life-threatening Hospitalization-initial or prolonged Disability or permanent damage Congenital anomalies or birth defects Other medically important condition	dd/mmm/yyyy/ dd/mmm/yyyy		dd/mmm/yyyy

Programming Note: Sorted by Group, Subject ID.
<Program Name: Time and Date>

Listing 14: Serious Adverse Events – ITT Population (continued)

Subject Number	SAE Name	Hospitalized Date	Discharge Date	Continued Study Participation	Outcome	Relationship to Study Drug	Important Medical Event?
xx	Verbatim text	dd/mmm/yyyy	dd/mmm/yyyy	Y/N	Resolved Resolved with sequelae	Unrelated Unlikely Possibly Related Probably Related Definitely Related	

Programming Note: Sorted by Subject Number.
<Program Name: Time and Date>

Listing 15: Concomitant Medications – ITT Population

Subject Number	Prior Med?	Verbatim Medication Name	Indication	Route	Dose	Frequency	Start Date	Stop Date
xxx	Y N	xxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx	dd/mmm/yyyy	dd/mmm/yyyy or Ongoing

Programming Note: Sorted by Subject Number, Start Date.
<Program Name: Time and Date>