STATISTICAL ANALYSIS PLAN

Official Title: A Double-blind Randomized Controlled Trial to Assess the Lot-to-lot Consistency of Sci-B-Vac™ in Adults (CONSTANT)

Protocol Identifying Number: Sci-B-Vac–002

NCT Number: NCT03408730

Version: 2.0

Date of Version: December 4, 2019

Study Sponsor:
VBI Vaccines Inc.
310 Hunt Club Road East Ottawa, ON K1V 1C1 Canada
Telephone: (613) 749-4200

STATISTICAL ANALYSIS PLAN

Sci-B-Vac-002

A Double-blind Randomized Controlled Trial to Assess the Lot-to-lot Consistency of Sci-B-Vac™ in Adults (CONSTANT)

Version: Final 2.0

Date: 04/Dec/2019

REVISION HISTORY

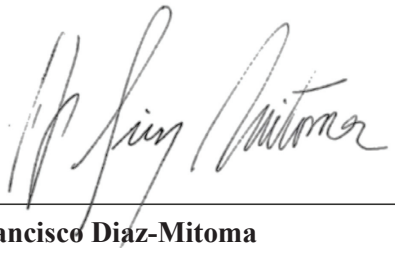
Version	Version Date	Author	Summary of Changes Made
Draft 1.0	16May2017	Yongmei Zhou (Biostatistician)	New Document
Final 1.0	See Footer	Yongmei Zhou (Biostatistician)	1. Delete age derivation since date of birth is collected as MMYYYY 2. Wording to match protocol 3. Updated based on protocol version 2.0
Draft 1.1	See Footer	Hong Wang (Biostatistician)	1. Added bar plot of SPR on Days 168, Day 196 and 336 2. Clarified change from baseline for hematology and biochemistry calculated for SSA only 3. Added summary table for PE 4. Added Section 6.3.4 to define the nominal study visit and analysis visit 5. Updated the protocol version that this SAP is based on. 6. Corrected the typo of "Miettnen and Nurminen method" to "Miettinen and Nurminen method" 7. Clarified the TEAE definition to be consistent with 2nd safety endpoint in the protocol. 8. Updated the SAS version that will be used to version 9.3 or later. 9. Removed the appendixes because they are already included in the previous sections of the SAP.
Draft 1.2	See Footer	Hong Wang (Biostatistician)	1. Updated the sample size in Section 4 because the sponsor decided to close enrollment early 2. Removed the analysis for AESI because no Adverse Events of Special Interest was identified by the Sponsor 3. Added subgroup analysis by country/region for the assessment of consistency in treatment effects across countries/regions 4. Provided details how the immunogenicity data will be used to define seroprotection and how the upper limit value will be used as continuous variables

Version	Version Date	Author	Summary of Changes Made
			5. Added analysis for all AEs occurred from the date of first vaccination through the date of end study 6. Added an additional exploratory analysis per Sponsor's request as follows: To determine whether the SPR after 2 vaccinations with Sci-B-Vac™, evaluated 20 weeks after the second vaccination (just prior to receiving the third vaccination), is non-inferior to the SPR 4 weeks after receiving the third vaccination with Engerix-B®. 7. Added sensitivity analysis based on ITT in the secondary objective analyses
Draft 1.3	See Footer	Hong Wang (Biostatistician)	Removed the out of window at V2 as a major PD causing exclusion from PPS in Section 6.2.5. The sponsor doesn't think that it will affect immunogenicity analysis.
Draft 1.4	See Footer	Hong Wang (Biostatistician)	Added visit window for immunogenicity data per Sponsor's request
Draft 1.5	See Footer	Andreana Robertson	Modified PAREXEL signature page (changed biostatistician). Removed strikethroughs (text that should be deleted but wasn't marked for deletion in tracked-changes). Removed immunogenicity analysis visits description (which included Table 1) from Section 6.3.4; adjusted subsequent table numbers accordingly. Updated verbiage in Section 6.3.8 to clarify that disposition summaries are done overall as well as by treatment group, with the exception of screened and screen fail counts.
Draft 1.6	See Footer	Andreana Robertson	Added another per protocol set, PPS1 (no exclusions due to out-of-window visit 3 and/or visit 4) for primary endpoint analysis.
Final 2.0	See Footer	Andreana Robertson	Up-versioned to Final 2.0.

SIGNATURE PAGE - VBI VACCINES INC.

Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.



December 4, 2019

Dr. Francisco Diaz-Mitoma | **Date (DD Mmm YY)**

Chief Medical Officer

December 4, 2019

Dr. Vlad Popovic | **Date (DD Mmm YY)**

VP, Clinical Development and Medical Affairs

December 4, 2019

Johanna Spaans | **Date (DD Mmm YY)**

Clinical Epidemiologist

SIGNATURE PAGE - PAREXEL

Declaration

The undersigned agree to the statistical analyses and procedures of this clinical study.

If this document has been signed electronically, signature(s) and date(s) are present at the end of the document:

Document prepared and approved by:

Andreana Robertson, MS	**Date (DD Mmm YY)**
Principal Biostatistician	

TABLE OF CONTENTS

ABBREVIATION AND ACRONYM LIST

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
ANCOVA	Analysis of covariance
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
Bpm	Beats per minute
CI	Confidence interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
CVID	Common variable immune deficiency
DBP	Diastolic blood pressure
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FAS	Full analysis set
GMC	Geometric mean concentration
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HR	Heart rate
IP	Investigational Product
IWRS	Interactive web response system
LQ	Limit of quantification
MCAR	Missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
NK	Not known
NOCI	New onset of chronic illness
PD	Protocol deviation
PPS	Per Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation or single dose

Abbreviation / Acronym	Definition / Expansion
SE	Standard error of the mean
SOC	System Organ Class
SPR	Seroprotection rate
SSA	Sub-study Analysis Set
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
TLF	Tables, Listings and Figures
VBI	VBI Vaccines Inc
WHO-DD	World Health Organization - Drug Dictionary

STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP).

The analyses described are based on CSP V4.0, dated 09May2018.
The SAP will be finalized prior to database unblinding and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made and this SAP will be amended. Any deviations from the SAP after database unblinding, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in the clinical study report (CSR).

1. STUDY OBJECTIVES

1.1 Primary Objective

To demonstrate the manufacturing equivalence, in terms of immunogenicity, of three independent consecutive lots of the Sci-B-Vac™ 4 weeks after the third vaccination. This objective will be met if the following condition is satisfied:

- The upper and lower bound of the two sided 95% CI of the geometric mean concentration (GMC) of anti-HBs ratios 4 weeks after the third vaccination, for all three pairwise comparisons (GMC of anti-HBs in group A/GMC of anti-HBs in group B, GMC of anti-HBs in group A/GMC of anti-HBs in group C, GMC of anti-HBs in group B/GMC of anti-HBs in group C) are within [0.67, 1.5].

1.2 Secondary Objectives

Immunogenicity

To demonstrate that the SPR 4 weeks after completion of the three-dose regimen of Sci-B-Vac™ is non-inferior to a three-dose regimen of Engerix-B®, i.e. the lower bound of the 95% two-sided confidence interval (CI) of the difference between the SPR Sci-B-Vac™ arm minus the SPR in the Engerix-B® arm, achieved 4 weeks after the third vaccination will be > -5.

Safety

- To assess the safety and reactogenicity of Sci-B-Vac™ compared to Engerix-B®

1.3 Exploratory Objectives

The following are exploratory objectives:

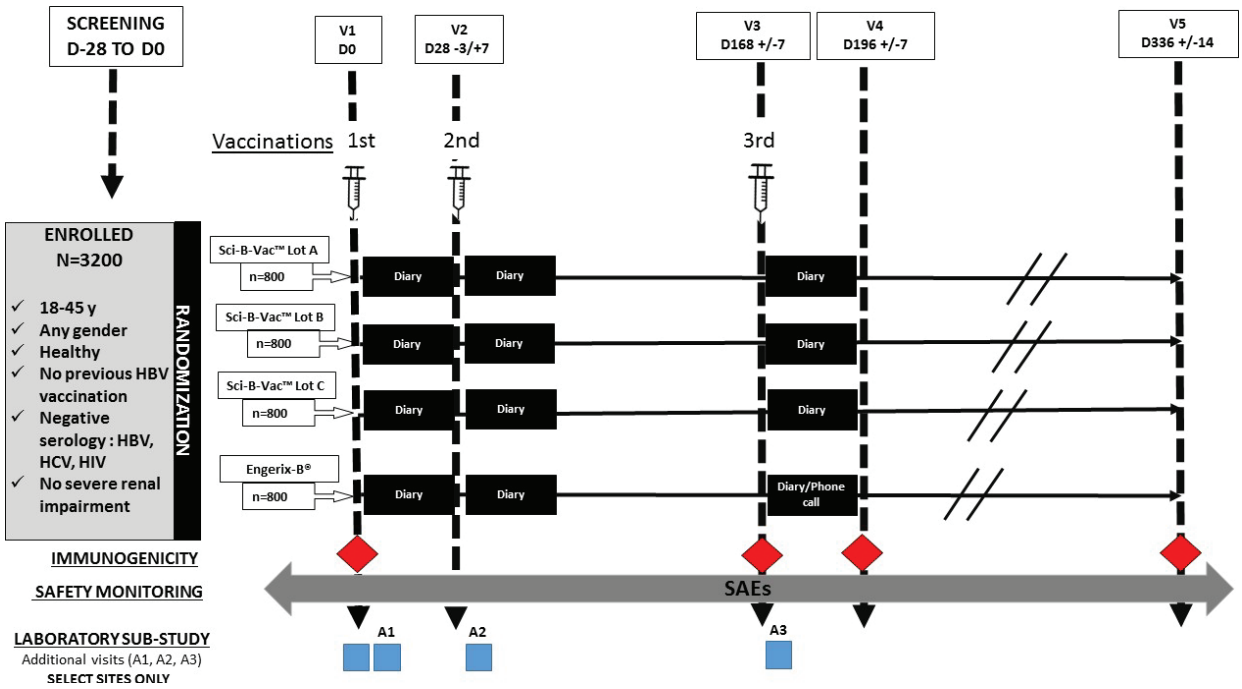
- To assess the Geometric Mean Concentration (GMC) of anti-HBs in serum after 2 vaccinations, just prior to receiving the third vaccination, and 24 weeks after the third vaccination with Sci-B-Vac™ or Engerix-B®, on Study Days 168 and 336, respectively.
- To assess the seroprotection rate after 2 vaccinations, just prior to receiving the third vaccination, and 24 weeks after the third vaccination with Sci-B-Vac™ or Engerix-B®, on Study Days 168 and 336, respectively. Seroprotection is defined as anti-HBs levels ≥ 10mIU/mL in serum. Seroprotection Rate (SPR) is the percentage (%) of subjects achieving seroprotection.
- To assess the Proportion of subjects achieving anti-HBs levels ≥ 100mIU/mL in serum, as a measure of an especially robust immune response, on Study Days 168 and 196, just prior to and 4 weeks after the third vaccination with Sci-B-Vac™ or Engerix-B®, and on Study Day 336.
- To assess the rate of non-response on Study Day 196, 4 weeks after the third vaccination with Sci-B-Vac™ or Engerix-B®. Rate of non-response is defined as the proportion of subjects not attaining anti-HBs levels ≥ 10mIU/mL in serum.
- To assess SPR, GMC and rate of non-response in sub-groups of interest (e.g. BMI > 30), 4 weeks after receiving the third vaccination with Sci-B-Vac™ or Engerix-B®.
- To determine whether the SPR after 2 vaccinations with Sci-B-Vac™, evaluated 20 weeks after the second vaccination (just prior to receiving the third vaccination), is non-inferior to the SPR 4 weeks after receiving the third vaccination with Engerix-B®.

2. STUDY DESIGN

This is a double-blind 4-arm randomized study. Subjects age 18-45 years will be randomly assigned to one of 3 lots of Sci-B-Vac™ or to Engerix-B® with a ratio 1:1:1:1 using a web-based randomization system to be immunized against Hepatitis B virus (HBV), according to a three-dose immunization schedule and followed for 24 weeks after the third immunization. The total study duration for each subject (assuming a screening period of 28 days or 4 weeks) is 364 days or 52 weeks.

The scheme of the study design is as Figure 1. For further details please refer to section 3.1 of the Protocol.

Figure 1: Schematic of Study Design



3. STUDY POPULATION

Per protocol, the study population will consist of approximately 3200 adult subjects (18-45 years) in at least 30 study centers in the E.U., Canada and the U.S. of all races and ethnic groups meeting all the inclusion criteria and none of the exclusion criteria. The final study population consisted of approximately 2800 adult subjects after an early closure to enrollment (see Section 4).

Inclusion criteria

Subjects must meet all the following criteria:

1. Any gender.
2. Age 18-45 years.
3. Healthy, as determined by a physical examination and values of laboratory tests.
4. If female: a) either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), OR b) is of childbearing potential and must agree to use an adequate birth control method during the screening period and until the end of her participation in the study (effective birth control includes: 1) hormonal

(implant, oral, vaginal, transdermal) contraceptives; 2) diaphragm with spermicide, condom (with or without spermicide); 3) intra-uterine devices; and 4) vasectomy of male partner; 5) abstinence from penile-vaginal intercourse (if the preferred and usual lifestyle of the subject)).

5. Able and willing to give informed consent.

Main Exclusion criteria

Main exclusion criteria are listed below, for the complete list of exclusion criteria please refer to section 4.1.2 of the Protocol. Participants meeting any of the exclusion criteria will be excluded.

1. Previous vaccination with any HBV vaccine (licensed or experimental).
2. Treatment by immunosuppressant within 30 days of enrollment including but not limited to corticosteroids at a dose that is higher than an oral or injected physiological dose, or > 20 mg /day prednisolone equivalent (Inhaled and topical steroids are allowed).
3. History of immunological function impairment, including but not limited to: a) autoimmune diseases (e.g., multiple sclerosis, type 1 diabetes, myasthenia gravis, Crohn disease and other inflammatory bowel diseases, celiac disease, systemic lupus erythematosus, scleroderma, including diffuse systemic form and CREST syndrome, systemic sclerosis, dermatomyositis polymyositis, rheumatoid arthritis, juvenile idiopathic arthritis, autoimmune thyroiditis -including Hashimoto thyroiditis, Grave's or Basedow's disease, immune thrombocytopenic purpura, autoimmune hemolytic anemia, autoimmune hepatitis, psoriasis, vitiligo, vasculitis, Guillain-Barré syndrome, Addison's disease, Bell's Palsy and Alopecia Areata);

   b) secondary immunodeficiency disorders (e.g. Acquired Immunodeficiency Syndrome caused by Human Immunodeficiency Virus infection (HIV/AIDS), solid organ transplant, splenectomy);

   c) primary immunodeficiency disorders (e.g. common variable immune deficiency (CVID), Defective phagocytic cell function and neutropenia syndromes, complement deficiency).
4. Pregnancy or breastfeeding.
5. Immunization with attenuated vaccines (e.g. MMR) within 4 weeks prior to enrollment.
6. Immunization with inactivated vaccines (e.g. influenza) within 2 weeks prior to enrolment.

4. STATISTICAL BASIS FOR SAMPLE SIZE

The sample size for this study is driven by the lot-to-lot consistency requirement. A total of 800 subjects in each of the three Sci-B-Vac™ lots will provide at least 90% power to ensure that the 95% confidence interval for each pairwise difference (GMC of anti-HBs in group A/GMC of anti-HBs in group B, GMC of anti-HBs in group A/ GMC of anti-HBs in group C, GMC of anti-HBs in group B/ GMC of anti-HBs

in group C) in normalized log10 (GMC) will have a lower bound that is >-0.176 and an upper bound that is <0.176 if the true standard deviation is ≤0.9; this corresponds to the true GMC ratio falling between 2/3 and 3/2. With an active comparator arm of Engerix-B® of equal size (n=800), the total sample size of the study is 3,200.

If lot-to-lot consistency is demonstrated, all three Sci-B-Vac™ lots will be pooled together to test that the Seroprotection Rate (SPR) four weeks after completion of the three-dose regimen of Sci-B-Vac™ is non-inferior to a three-dose regimen of Engerix-B®. Assuming 10% of the subjects are non-evaluable (i.e., 2880 are evaluable, with 2160 randomized to Sci-B-Vac™ and 720 to Energix-B®), a two-sided 5% significance level and a non-inferiority margin of – 5%, the non-inferiority test will have > 90% power. The following table provides the estimated power under different assumptions of the SPR four weeks after completion of the three-dose regimens.

Response in Energix-B® (N=720)	Response in Sci-B-Vac™ (N=2160)	Power
80%	85%	99%
85%	85%	92%
90%	95%	99%

In October 2018, enrollment was closed early for non-safety-related reasons after 2838 were randomized to the study. With approximately 700 subjects in each of the three Sci-B-Vac™ lots and 700 subjects in comparator arm of Engerix-B®, the sample size will provide > 80% power to evaluate both the primary objective of lot to lot consistency of the three Sci-B-Vac lots, and the secondary objective of non-inferiority of Sci-B-Vac™ vs Engerix-B®.

5. RANDOMIZATION

A statistician who is not involved in the clinical aspects of the study will generate a permuted blocked randomization list for each site. Randomization will be via a web-based IWRS, stratified by study center. The site pharmacy and/or unblinded study center staff will receive a notification of the randomization, which should be filed in a locked area/ computer folder not accessed by blinded study center staff.

5.1 Definition of Vaccination/Randomization Errors

The list below provides some examples of potential errors that may occur during vaccination:

- Subjects vaccinated with a Sci-B-Vac™ lot different from the one assigned Sci-B-Vac™ lot at randomization.
- Subjects vaccinated with the correct Sci-B-Vac™ lot but containing a lower volume.
- Subjects vaccinated with a vaccine different from the one assigned at randomization.

Please see section 6 of this document for a complete guidance on how vaccination/randomization errors are handled in the statistical analysis.

6. STATISTICAL ANALYSIS CONVENTIONS

6.1 Analysis Variables

Baseline characteristics, medical history, vaccination, immunogenicity (measurement of anti-HBs), concomitant medication, adverse events (AEs) and other safety assessments will be assessed according to the schedule of events listed as following:

	Screening Visit	V1	Safety Follow-up Phone Call	V2	Safety Follow-up Phone Call	Safety Follow--up Phone Call	V3	Safety Follow-up Phone Call	V4 (I)	V5 End of Study Visit
Timelines (days)	-28	0		28			168		196	336(a)
Range (days)	-28 to 0		V1 + 5-9	-3/+7	V2 + 5-9	V2 +21-35	+/-7	V3 + 5-9	+/-7	+/-14
Screening										
Informed Consent	X									
Physical Exam (b)	X	X		X			X		X	X
Medical History	X									
Height and weight	X									
Medications	X									
HBV serology	X									
HIV and HCV serology	X									
Urine Pregnancy test	X	X		X			X			
Serum chemistry, hematology, HbA1C	X									
Urinalysis	X									
Inclusion & Exclusion Criteria	X									
Confirmation of enrollment	X	X								
Vaccination		X		X			X			
Immunogenicity		X (c)					X (c)		X	X
Safety Assessments										
Vital signs	X	X (d)		X (d)			X (d)		X	
Subject instructed to complete diary		X	X	X	X		X	X		
Local & Systemic Reactions		X	X(e)	X	X(e)	X(e)	X	X(e)		

Unsolicited Non Serious AEs		X	X(g)	X(g)	X(g)	X(g)	X(f)	X(g)	X(g)	X(f)
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events, Medically significant event and NOCI (h)	Continuous									
Sub-Study (select sites)			A1*		A2*			A3*		
Serum chemistry, hematology		X (c)	X(j)		X(j)			X(j)		
	(a) Or earlier in case of withdrawal (reason for withdrawal to be documented in eCRF) (b) Full physicals to be done at screening or pre-vaccination at Day 0. History-directed physicals can be completed at subsequent visits. (c) Blood sample will be taken before vaccination (d) Vital signs will be recorded before and 30 minutes after each vaccination. (e) Subjects will be instructed to record solicited and unsolicited AEs. There will be a telephone call 7 days (+/-2 days) after each vaccination, and 28 days (+/- 7 days) after the second vaccination to inquire about AEs. If there is a reaction the subject may be asked to come for a supplemental visit (not represented in this table) to assess severity at the discretion of the investigator. Follow-up until resolution. (f) Only AEs requiring medical attention (g) All AEs (h) NOCI = new onset of chronic illness (i) Visit 4 should be scheduled at least 3 weeks after Visit 3 (j) Blood sample collected 7 days (-3/+7 days) after vaccination *Additional visits (A1, A2 and A3) required for study subjects **at select sites** participating in the clinical laboratory sub-study.									

6.1.1 Derived and Computed Variables

Demographics

Body Mass Index (BMI, kg/m^2) will be calculated using the following formula:

BMI = Weight (kg) / Height^2 (m^2)

Immunogenicity

Values below the lower limit of quantification (recorded as "< LQ") will be set to half that limit (LQ/2).
Values above the upper limit of quantification (recorded as ">UQ") will be set to that upper limit (UQ).

Titer greater or equal to a given threshold is defined as binary variable for non-missing values as:

= 1, if the titer is superior or equal to the given threshold
= 0, otherwise

Seroprotection is defined as binary variable for non-missing values as:

= 1, if anti-HBs levels ≥ 10mIU/mL in serum
= 0, otherwise

Seroprotection rate (SPR) is the percentage (%) of subjects achieving seroprotection.

An initial result of >=5.0 and <12.0 mIU/mL ("Indeterminate") required duplicate retest per Laboratory Procedure Manual. In the statistical analysis, if the anti-HBs serology result is initially indeterminate, then the average of initial and repeat samples will be calculated. Seroprotection will be determined as follows: if the average of initial and repeat samples is ≥10 mIU/mL, then it will be considered seroprotected. If it is less than 10 mIU/mL will be considered not seroprotected.

Geometric Mean Concentration

The GMC will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers/concentrations.

Solicited Adverse Events

Reactions at the site of injection (redness/erythema, pain, tenderness, swelling/edema, pruritus), systemic reactions (nausea/vomiting, diarrhea, headache, fatigue, myalgia) and vital signs abnormalities (fever, tachycardia, bradycardia, hypertensions, hypotension, changes in respiratory rate).

Unsolicited Adverse Events

All adverse events will be characterized according to the date of occurrence related to the vaccination phase as follows:

- **Emergence before vaccination phase**: start date before the first date of injection of study vaccine.
- **Emergence during vaccination phase**: start date on or after the first date of injection of study vaccine or, adverse event increase in severity including to "serious" adverse event.

If an adverse event start date is equal to the first date of vaccination injection, missing or unknown, the adverse event will be considered as emergent.

When start and/or end dates of an adverse event are only partially known, adverse events will be categorized as emergent before, during (or after) vaccination phase using the following rules:

- If the partial end date is before (<) the first study vaccination (i.e., year or year & month is/are before the first study vaccination year or year & month) then the adverse event is emergent before vaccination phase.

- If the partial start date is equal or after (≥) the first study vaccination (i.e., year or year & month is/are after or the same as the first study injection year or year & month) then the adverse event is emergent during vaccination phase.

The **maximum event severity** is the greatest severity associated with a preferred term for a reported adverse event according to the following order: Mild < Moderate < Severe < Potentially life threatening. Unknown/ Missing severity is considered as potentially life threatening.

Multiple AEs with the same PT for the same subject are counted only once.

Vaccination-related Adverse Events are those for which the cause has been evaluated by the investigator, and recorded either as very likely/certain, possibly related, probably related or unknown/ missing.

Pre-study, Concomitant and Post-Study Medications

A **pre-study medication** is a medication used only before the first study vaccination (i.e. medication end date < first study vaccination date).

A **post-study medication** is a medication used only after study termination (i.e. medication start date > study termination date). This will not be collected in the clinical database and will not be reported in the CSR.

All other medications are **concomitant**.

When start and/or end dates of a medication intake are missing, the medication is considered as concomitant with the study vaccination schedule.

If the first study vaccination date is missing then the medication is considered as concomitant with the study vaccination schedule, provided that the study vaccine was administered to the subject.

6.2 Analysis Sets

6.2.1 All Enrolled Set

The All Enrolled Set will be defined as all screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study.

6.2.2 Safety Set

All subjects in the All Enrolled Set who receive a study vaccination. Subjects will be analyzed as vaccinated, i.e., a subject will be assigned according to the vaccination received.

In case of vaccination error, subjects will be analyzed as initially "treated" (i.e., according to the first vaccine a subject receives, rather than the vaccine to which the subject is randomized).

6.2.3 Intent-to-Treat (ITT)

All subjects in the All Enrolled Set who were randomized.

In case of vaccination error, subjects in the ITT will be analyzed "as randomized" (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received). Any subject who received the wrong vaccination will not be excluded from the ITT.

6.2.4 Full Analysis Set (FAS)

All subjects in the All Enrolled Set who receive at least one vaccination and provide at least one evaluable serum immunogenicity sample both at baseline and after baseline.

In case of vaccination error, subjects in the FAS will be analyzed "as randomized" (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received). Any subject who received the wrong vaccination will not be excluded from the FAS.

If a subject is unblinded during the study, he/she will be included in the FAS.

6.2.5 Per Protocol Sets

6.2.5.1 Per Protocol Set 1 (PPS1)

All subjects in the FAS who:

- received all 3 vaccinations
- have an evaluable serum immunogenicity samples at baseline and at the time point of interest
- are seronegative at baseline
- had no major protocol deviations leading to exclusion, which will be identified prior to unblinding.

A major protocol deviation for the purpose of exclusion from the PPS1 is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity result of the subject. These will be identified prior to unblinding and analysis and may include:

- subjects enrolled who did not meet study entry criteria
- subjects who did not receive the correct treatment
- subjects who developed withdrawal criteria but were not withdrawn
- subjects who received a prohibited concomitant medication

- subjects with a deviation identified through monitoring visits or otherwise, where the deviation is judged to impact the reliability of subject immunogenicity results

PPS1 will be used for the primary endpoint analysis.

6.2.5.2 Per Protocol Set 2 (PPS2)

All subjects in PPS1, but excluding those who attended study visits outside of the following windows:

- V3/Day 168 (+/- 28 days)
- V4/Day 196 (-7/+14 days)

PPS2 will be used for the primary, secondary, and exploratory endpoints.

In case of vaccination error, subjects in PPS1 and/or PPS2 will be analyzed "as randomized" and the subject who received the wrong vaccination will be excluded from PPS1 and/or PPS2. If a subject receives a vaccine from the wrong kit number, but the same as the one the subject was randomized to, the subject will not be removed from PPS1 and/or PPS2.

If a subject is unblinded during the study, except for suspected unexpected serious adverse reaction (SUSAR), he/she may be excluded from PPS1 and/or PPS2 based on sponsor's decision with respect to any potential bias that may be introduced in the analysis of the primary and key secondary immunogenicity analyses.

6.2.6 Sub-study Analysis Set (SSA)

All subjects in the All Enrolled Set who actually receive at least one dose of study vaccination and participated in the clinical laboratory sub-study.

6.2.7 Sub Groups

The following key sub-groups of interest will be pre-specified:

- Gender (male vs female)
- BMI (≤ 30 vs > 30)
- Smoking Status (current vs past or non-smoker)
- Daily alcohol consumption (≥4 drinks/day vs 2-3 drinks/day vs 0-1 drink/day)
- Non-study licensed vaccine (no vaccination vs vaccination)
- Race (White vs Black or African American vs Other)
- Ethnicity (Hispanic or Latino vs Non Hispanic or Latino)
- Country/region (United States vs Canada vs Europe)

6.3 Statistical Analysis Methods

6.3.1 Listings and Descriptive Statistics

All original and derived parameters as well as population characteristics will be listed and described using summary statistics. Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). All listings will include repeated and unscheduled measurements.

All descriptive statistics will be presented by lot and treatment and visit. The baseline for all measurements (where applicable) will be the last pre-vaccination measurement. Descriptive statistics for all data obtained at Screening and follow-up will be presented separately.

6.3.2 Statistical Significance Level

All statistical tests will be two-sided and will be performed at the 5% level of significance, unless otherwise stated.

6.3.3 Software

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.3 or later.

6.3.4 Study Visits

For laboratory data, vital sign data and physical examination data, data will be summarized or listed using the scheduled visits (See Table 1).

Table 1: Study Visits and Analysis Visits

Nominal Study Visit	Analysis Visit	Target Study Day*
Screening	Screening	-28
Visit 1	Day 0	1
Visit A1	Day 7	8
Visit 2	Day 28	29
Visit A2	Day 35	36
Visit 3	Day 168	169
Visit A3	Day 175	176
Visit 4	Day 196	197
Visit 5	Day 336	337
Unscheduled	Unscheduled	

* Study Day 1 is the date of first vaccination is administered to the subject. Study Day = (date of event/visit – first vaccination date) if it is before the first vaccination. Study Day = (date of event/visit – first vaccination date) + 1 if it is on or after the first vaccination.

Unscheduled assessments will be included in listings, but not in summaries. If a subject has multiple assessments within the same post-baseline analysis visit, the following rules will be established to select the data to be included in the descriptive summary:

- If multiple assessments occur within a given analysis visit, the assessment closet to the target study day will be used for analysis purposes.
- If there are 2 or more values equal distance to the target study day, then the last assessment, within the analysis visit, will be used in the analysis.

6.3.5 Missing Data

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, each of immunogenicity analyses will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

6.3.6 Interim Analysis

Not applicable.

6.3.7 Protocol Deviations

6.3.7.1 Definition of Protocol Deviation

Deviations from the protocol will be assessed as 'minor' or 'major'. CSR reportable ("major") protocol deviations (PDs) are defined in accordance with ICH E3 as important PDs related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment resulting in the potential to jeopardize the safety or rights of the trial subjects or the scientific value of the trial.

All major PDs will be classified into the following categories, but not all deviations listed below will necessarily be declared a major PD:

▫ Informed Consent

▫ Inclusion/Exclusion criteria

▫ Withdrawal Criteria

▫ Investigational Product (IP) Admin/Study Treat

▫ Disallowed Medications

▫ Adverse Event (AE)/ Serious Adverse Event (SAE)

- Visit Schedule
- Procedure/Tests

Major PDs may result in exclusions of subject from one or more analysis sets according to study-specific PD codes specifications. Major protocol deviations that may lead to exclusion of the subject from PPS1 and/or PPS2 are defined in Section 6.2.5.

The following PD summaries will be provided:

- Number and percentage of subjects with a major protocol deviation by type of deviation and vaccine group

A by-patient listing of protocol deviations will be provided.

6.3.7.2 Determination of Protocol Deviations

Prior to unblinding, a PD report will be provided to the Clinical Study Team (CST) consisting of medical, clinical, and operational team members from the Sponsor and CRO for review on an ongoing basis during the study. The PDs review is part of the Data Listing Review process.

After the review, the CST team is responsible for assessing the impact of PDs on the immunogenicity and safety data for study subjects from medical and clinical perspectives. The PDs will be identified and categorized to determine subjects to be excluded from analysis populations according to the PDs specification.

Details of PD review procedure will be provided in the Medical Monitoring Plan and Data Listing Review Manual.

6.3.7.3 Exclusions of Individual Values for Safety Analysis

Some local and systemic adverse events (AEs) will be directly measured by the subject and will not be subject to a reconciliation process, even if they are biologically implausible. Therefore, these implausible measurements will be removed from the analysis but included in listings. Implausible measurements are summarized in the Table 2 below:

Table 2: Implausible Solicited Adverse Events

Parameter	Implausible measurements
Body temperature	≤ 33°C or ≥ 42°C
Erythema/Redness	Measurements ≥ 900 mm or Measurements < 0 mm
Induration/Swelling	Measurements ≥ 500 mm or Measurements < 0 mm

6.3.8 Subject Disposition

The following subject data will be presented overall as well as by Sci-B-Vac™ lot, Sci-B-Vac™ treatment group and Engerix-B® treatment group (where possible):

- The number of subjects screened (overall counts only)
- The number of screen failures with a breakdown of reasons for screen failure (overall counts only)
- The number of subject randomized
- The number of subjects dosed.
- The number and percentage of subjects who completed treatment
- The number and percentage of subjects who discontinued from treatment with a breakdown of primary reasons for discontinuation from treatment
- The number and percentage of subjects who completed study
- The number and percentage of subjects who terminated early. The number and percentage of subjects who withdrew early from study with a breakdown of primary reasons for the early withdrawal.

Percentages of subjects will be based on the number of subjects dosed as 100%. All enrolled set will be used for subject disposition.

In addition, by-subject listings will be provided for subjects who discontinued the study early with reason for discontinuation.

6.3.9 Demographic Data

All demographic data will be presented for the ITT, FAS, PPS1, PPS2, Safety Set and SSA. All demographic and baseline characteristics will be listed and summarized by Sci-B-Vac™ lot, Sci-B-Vac™ treatment group and Engerix-B® treatment group using appropriate descriptive statistics. Continuous data will be summarized using the number of observations, mean, standard deviation, median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. No statistical hypothesis testing will be conducted.

6.3.10 Medical History

The frequencies and percentages of subjects with medical history will be presented by MedDRA system organ class and preferred term, by Sci-B-Vac™ lot, Sci-B-Vac™ treatment group and Engerix-B® treatment group. Medical history data will be tabulated for the ITT, FAS, PPS1, PPS2 and Safety Set.

6.3.11 Concomitant Medication

Concomitant medication will be summarized and listed for Safety Set. The frequencies and percentages of subjects reporting concomitant medications will be tabulated by Sci-B-Vac™ lot, Sci-B-Vac™ treatment group and Engerix-B® treatment group. Medications (generic drug name) will be coded using the WHO Drug dictionary.

Prior and concomitant procedures/non-drug therapies will be presented in a listing.

6.3.12 Exposure to the Investigational Medicinal Product

The number of subjects actually receiving the first, second and the third vaccination and the number of subjects received only 1 vaccination, only 2 vaccinations and all three vaccinations will be summarized by Sci-B-Vac™ lot, Sci-B-Vac™ treatment group and Engerix-B® treatment group for safety population.

Vaccine administration information will also be listed.

6.3.13 Immunogenicity

The primary analysis of the immunogenicity data will be based on PPS1 and PPS2. Sensitivity analyses using the same modeling approach will be conducted using the FAS. These analyses will be reported both with and without patients in the FAS who are seropositive at baseline.

Immunogenicity (measurement of anti-HBs titer) data will be listed by subject including actual sampling times relative to dosing. Serum concentrations will be summarized by Sci-B-Vac™ lot, Sci-

B-Vac™ treatment group and Engerix-B® treatment group. The following descriptive statistics will be presented for serum concentrations obtained at each time point: n, geometric mean, geometric SD, median, minimum and maximum values.

Individual serum concentration versus actual times will be plotted by Sci-B-Vac™ lot, Sci-B-Vac™ treatment group and Engerix-B® treatment group for anti-HBs antibody in linear and semi-logarithmic scale. The geometric mean serum concentrations with corresponding 95% confidence intervals versus times will also be presented . The bar plot of SPR by treatment on Days 168, 196 and 336 will also be produced based on PPS2. All treatment groups will be overlaid on the same plot.

6.3.13.1 Primary Hypothesis

The lot-to-lot equivalence, in terms of immunogenicity, of three independent consecutive lots of the Sci-B-Vac™ will be demonstrated if the following condition is satisfied:

The upper and lower bound of the two sided 95% CI of the geometric mean concentration (GMC) of anti-HBsAg antibody ratios 4 weeks after the third injection for all three pairwise comparisons (GMC(group A)/GMC(group B), GMC(group A)/GMC(group C), GMC(group B)/GMC(group C)) are within [0.67, 1.5]

The analysis will use a two-sided 5% significance level. PPS1 and PPS2 will be used to test the primary hypothesis.

6.3.13.2 Statistical Methods for Primary Immunogenicity Analyses

Geometric mean concentration (GMC) of anti-HBsAg antibody ratios 4 weeks after the third injection

All statistical analyses will be performed on the logarithmically (base 10) transformed values.

Adjusted estimates of GMCs and their associated 95% CIs will each be determined using an analysis of covariance (ANCOVA) model with a factor for vaccine lot group, and a covariate for the log transformed pre-vaccination (baseline) titer. Data from all centers will be pooled. For each vaccine lot, antibody GMCs, associated standard errors, two-sided 95% CIs and median, minimum, and maximum titer values will be determined and presented by lot group. The median, minimum, and maximum values will be reported on the actual titer values, rather than the log scale. The ratio in GMCs between each vaccine lot group (GMC(group A)/GMC(group B), GMC(group A)/GMC(group C), GMC(group B)/GMC(group C)), and their associated two-sided 95% CIs will also be presented.

Sensitivity analyses using the same modeling approach outlined above will be conducted using the FAS. These analyses will be reported both with and without patients in the FAS who are seropositive at baseline.

If this condition is satisfied with either PPS1 or PPS2, then manufacturing equivalence (lot-to-lot consistency) will be demonstrated.

Sample SAS code for assessment of lot-to-lot equivalence:

- Sample SAS code for ANCOVA model:

```
PROC MIXED;
CLASS treatment;
MODEL log (var) = treatment log (baseline of var);
        LSMEANS treatment / DIFF CL ALPHA=0.05;
        ODS OUTPUT LSMEANS=ls_means Diffs=diff;
QUIT;
```

where var represent the anti-HBs titer and treatment represents vaccine lot group.

6.3.13.3 Secondary Objective Analyses

If lot-to-lot consistency is demonstrated, then the data from the three lots will be combined to address the secondary immunogenicity non inferiority-hypothesis. It is to demonstrate that the SPR 4 weeks after completion of the three-dose regimen of Sci-B-Vac™ is non-inferior to the SPR 4 weeks after completion of a three-dose regimen of Engerix-B®. Seroprotection is defined as anti-HBs levels ≥ 10mIU/mL in serum. Seroprotection rate (SPR) is the percentage (%) of subjects achieving seroprotection.

Seroprotection rate (SPR) 4 weeks after the third injection

Non-Inferiority of Sci-B-Vac™ 4 weeks following the third vaccination compared to Engerix-B® 4 weeks following the third vaccination will be assessed using PPS2. Data from all centers will be pooled and data from all 3 lots of Sci-B-Vac™ will be pooled. The difference in proportions [SPR(Sci-B-Vac™) –SPR(Engerix-B®)] and two-sided 95% CIs, will be calculated using the Miettinen and Nurminen method. Funnel plot will be produced to investigate the impact of center.

Sample SAS code for assessment of non-inferiority:

- Sample SAS code for the analysis of binary data:

```
PROC FREQ; * specify and sub-select data set as applicable;
     TABLES trt*seroprotection/riskdiff (cl=mn); * numerical 0/1-scores identify 'event';
RUN;
```

where seroprotection represent the seropositive event and trt represents treatment group.

If the lower bound of the 95% Miettinen-Nurminen CI is greater than -5%, Sci-B-Vac™ will be declared non-inferior to Engerix-B®.

Sensitivity analyses using the same modeling approach outlined above will be conducted using the FAS and ITT. For these ITT analyses, patients with missing data at Day 196 (4 weeks following the third vaccination) will be included and treated as failures. These analyses will be reported both with and without patients who are seropositive at baseline.

6.3.13.4 Exploratory Objective Analyses

Analysis of all exploratory immunogenicity endpoints will be based on PPS2, unless otherwise indicated. Exploratory efficacy endpoints will be summarized and analyzed without adjustment for multiple comparisons.

Each of the exploratory endpoints defined in the protocol will be summarized for each Sci-B-Vac™ lot separately, as well as for the difference between each Sci-B-Vac™ lot. Analysis of GMC endpoints will use the same methods as described above for the primary endpoint. For binary data, proportions and two-sided 95% CIs will be reported. The difference in proportions and two-sided 95% CIs, will be calculated using the Miettinen and Nurminen method.

In addition, each of the exploratory endpoints will be summarized with data from all 3 lots of Sci-B-Vac™ pooled together. Summaries will be presented for Sci-B-Vac™, Engerix-B™ and for the treatment difference. Adjusted estimates of GMCs and their associated 95% CIs will each be determined using an analysis of covariance (ANCOVA) model with a factor for treatment group, and a covariate for the log transformed pre-vaccination (baseline) titer. For each treatment group, anti-HBs GMCs, associated standard errors, two-sided 95% CIs and median, minimum, and maximum titer values will be determined and presented by treatment group. The median, minimum, and maximum values will be reported on the actual titer values, rather than the log scale. The ratio in GMCs between treatment groups (GMC of anti-HBs in Sci-B-Vac™ / GMC of anti-HBs in Engerix-B®), and their associated two-sided 95% CIs will also be presented. For binary data, proportions and two-sided 95% CIs will be reported. The difference in proportions and two-sided 95% CIs, will be calculated using the Miettinen and Nurminen method.

Please see Section 6.3.13.2 and Section 6.3.13.3 for sample codes. Per sponsor's request, one additional pre-specified exploratory analysis has been added to the SAP. This additional exploratory analysis is as follows:

- To determine whether the SPR after 2 vaccinations with Sci-B-Vac™, evaluated 20 weeks after the second vaccination (just prior to receiving the third vaccination), is non-inferior to the SPR 4 weeks after receiving the third vaccination with Engerix-B®.

This additional exploratory analysis will be summarized with data from all 3-lots of Sci-B-Vac™ pooled together.

6.3.14 Safety Analysis

The analysis of laboratory variables will be analyzed based on SSA. The analysis of the rest safety variables will be based on the Safety Set. Data from each Sci-B-Vac™ lot will be presented both individually as well as pooled together, while data from Engerix-B® will be presented separately.

6.3.14.1 Completer Analysis on Solicited Adverse Events

Solicited adverse events

The safety completeness analysis on solicited adverse events aims to identify subjects who completed diary cards and/or remained in clinic for at least 30 minutes post vaccination, irrespective of severity. The analysis will show the number of subjects with valid data by solicited adverse event and time point. Valid data in the context of the safety completeness analysis are all data entered in the diary card and/or 30 minutes post each vaccination assessment (including implausible values) except "Not done/unknown".

Three summaries will be produced:

1. The frequencies of subjects who provide diary cards by vaccine group.

2. For each type of solicited adverse event (local, systemic, other), the frequencies of subjects with valid data by vaccine group, aggregated over time points and intervals: 0-30 min (clinic), >30 min – Day 1 (diary), Day 2 – 7 (diary). where the Day 1 is the date of each vaccination. The Day value is incremented by 1 for each date following the date of the vaccination.

3. For each solicited adverse event, the frequencies of subjects with valid data by vaccine group aggregated over time points and intervals: 0-30 min (clinic), >30 min – Day 1 (diary), Day 2 – 7 (diary) where the Day 1 is the date of each vaccination. The Day value is incremented by 1 for each date following the date of the vaccination.

For the corresponding percentages, the denominator will be the respective numbers of exposed subjects, i.e., subjects who received a vaccination, irrespective of whether a diary card was present or not. All analyses will be based on the Safety Set (i.e. 'as treated').

6.3.14.2 Solicited Local, Systemic and Other Adverse Events

The following solicited local and systemic adverse events as well as solicited other adverse events will be collected. The grading of severity will be graded according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007) – also see protocol Appendix 2.

Solicited local adverse events:

- Redness/erythema
- Pain
- Swelling/edema
- Tenderness
- Pruritus

Injection site reactions grading				
	Grade 1	Grade 2	Grade 3	Grade 4
Pain (pain without touching)	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness (pain when area is touched)	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization

Pruritus associated with injection See also Skin: Pruritus (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

**In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.*
*** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.*

Solicited systemic adverse events:

- Nausea/vomiting
- Diarrhea
- Headache
- Fatigue
- Myalgia

The grading of systemic adverse events will be as follows:

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or > 2	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock

		episodes/24 hours		
Diarrhea	2 - 3 loose stools or < 400 g/24 hours	4 - 5 stools or 400 - 800 g/24 hours	6 or more watery stools or > 800g/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Solicited other adverse events:

- Fever
- Tachycardia - beats per minute (0-30 min only)
- Bradycardia - beats per minute (0-30 min only)
- Hypertension (0-30 min only)
- Hypotension (0-30 min only)
- Respiratory rate (0-30 min only)

The grading will be as follows:

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) *	38.0 – 38.4 00.4 – 101.1	38.5 – 38.9 101.2 – 102.0	1. 39.0 – 40 2. 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia

Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation
Subject should be at rest for all vital sign measurements. *** Oral temperature; no recent hot or cold beverages or smoking.* **** When resting heart rate is between 60 - 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.*				

All solicited AEs will be summarized according to defined severity grading scales. Frequencies and percentages of subjects experiencing each solicited AE will be presented for each symptom, by severity both overall and by time point (i.e., after each vaccination).

6.3.14.3 Unsolicited Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as those adverse events that either start or worsen on or after the date of first vaccination.

All following TEAEs will be included in the summary tables:

- All AEs occurred on the day of vaccination (vaccination 1, vaccination 2 or vaccination 3) and during the next 27 days [date of vaccination + 27 days]

  AND

- SAEs, medically significant events (i.e., AEs medically attended) or new onset of chronic illnesses through the date of end study

If a subject missed one or two vaccination injections, the AEs for the corresponding vaccination injections will not be included in the summary. For example, one subject missed vaccination 2, the AEs for the day of vaccination 2 and during the next 27 days will be missing and not be included in the summary tables and figures.

Solicited adverse events continuing beyond Day 7 will be coded by MedDRA and combined with the respective unsolicited adverse events.

For AEs included in the summary tables defined above, numbers of AEs will be summarized by System Organ Class (SOC) and Preferred Term, and also by severity/causality to vaccine. The summaries will be presented by vaccination (any vaccination, vaccination 1, vaccination 2 and vaccination 3) and interval of onset as follow:

- Day 1 to Day 28
  where the AEs will include AEs occurred on/after Day 1 (date of vaccination) until earliest date of (Day 28, date of next vaccination-1, end of study)
- Day 29 to end of considered interval
  where the AEs will include SAEs, medically significant events (i.e., AEs medically attended) or new onset of chronic illnesses occurred on/after Day 29 to earliest date of (date of next vaccination-1, end of study)
- Day 1 to end of considered interval
  where the AEs will include AEs occurred on/after Day 1 (date of vaccination) until earliest date of (date of next vaccination-1, end of study)

The original verbatim terms used by investigators to identify AEs in the eCRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The AEs will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. These summaries will be presented by treatment group and overall. When an AE occurs more than once for a subject, the maximal severity and strongest relationship to the treatment group will be counted. Separate summaries will be produced for the following categories:

- AEs
- SAEs
- Unexpected AEs
- AEs that are very likely, probably or possibly related to vaccine
- AEs leading to vaccine withdrawal
- AEs leading to study withdrawal
- AEs medically attended
- New onset of chronic illnesses
- Solicited AEs continuing beyond Day 7

In addition, all TEAEs occurred from the date of first vaccination through the date of end study will be summarized by MedDRA preferred terms into frequency tables according to system organ class for the following categories:

- AEs
- SAEs
- AEs leading to vaccine withdrawal
- AEs leading to study withdrawal
- New onset of chronic illness
- AEs medically attended

The following listings will be produced:

- All pre-vaccination AEs and TEAEs
- AEs leading to vaccine withdrawal
- AEs leading to study withdrawal
- SAEs
- AEs medically attended
- New onset of chronic illnesses
- Solicited AEs continuing beyond Day 7
- AEs leading to death

6.3.14.4 Clinical Safety Laboratory Tests (Hematology, Biochemistry and Urinalysis)

Laboratory values (hematology, biochemistry and urinalysis) will be listed by subject and study time point including changes from baseline (with the exception of urinalysis). The baseline for the laboratory values will be the latest non-missing result obtained before first vaccine injection.

All laboratory (e.g., hematology, biochemistry) data will be summarized using descriptive statistics. Summaries will be provided for the observed values and changes from baseline at each scheduled visit. The changes in biochemistry and hematology from baseline will only be calculated in the clinical laboratory sub-study analysis set (SSA). In addition, absolute and change from baseline values will be categorized according to the toxicity scales (See protocol Appendix 3 for laboratory parameters) and summarized by time point using shift tables.

6.3.14.5 Vital Signs

Vital signs data will be listed by subject including changes from baseline. The baseline for the vital signs measurements will be the latest non-missing results obtained before first vaccine injection.

All vital sign data will be summarized using descriptive statistics. Summaries will be provided for the observed values and changes from baseline at each scheduled visit. In addition, absolute and change from baseline values will be categorized according to the toxicity scales (see protocol Appendix 3 for vital signs) and summarized by time point using shift tables.

6.3.14.6 Physical Examination

The results of the physical examination will be listed by subject and time-point. Any clinically significant difference in physical examination from previous visit will be summarized by visit.

7. REFERENCES

1. SAS® Version 9.3 of the SAS System for Personal Computers. Copyright © 2002-2010. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
2. Protocol version 4.0

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UserName: Robertson, Andreana (robertan)
Title: Principal Biostatistician, GDO
Date: Wednesday, 04 December 2019, 11:50 PM GMT Standard Time
Meaning: Document contents approved.
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