STATISTICAL ANALYSIS PLAN

Official Title: A **P**hase 3 Double-Blind **R**andomized C**o**ntrolled **T**rial to Compare the Immunogenicity and Saf**e**ty of a Three-dose Regimen of Sci-B-Va**c**® to a **T**hree-dose Regimen of Engerix-B® in Adults (**PROTECT**)

Protocol Identifying Number: Sci-B-Vac–001

NCT Number: NCT03393754

Version: 4.0

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Study Sponsor:
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STATISTICAL ANALYSIS PLAN

Sci-B-Vac–001

A Phase 3 Double-Blind Randomized Controlled Trial to Compare the Immunogenicity and Safety of a Three-dose Regimen of Sci-B-Vac™ to a Three-dose Regimen of Engerix-B® in Adults (PROTECT)

Version: Final 4.0

Date: 13/May/2019

REVISION HISTORY

Version	Version Date	Author	Summary of Changes Made
Draft 1.0	16May2017	Yongmei Zhou (Biostatistician)	New document
Final 1.0	19Jul2017	Yongmei Zhou (Biostatistician)	1. Deleted the derivation for age since date of birth will be collected as MMYYYY 2. Updated the Appendix 1 3. Updated based on protocol version 2.0
Final 2.0	See Footer	Yongmei Zhou (Biostatistician)	1. added additional subgroups for age 2. added bar plot of SPR on Days 28, 56 and 196 3. clarify change from baseline for hematology and chemistry calculated for SSA1 only 4. added summary table for PE 5. deleted Section 8, 9 and 10 since they will be detailed in the mockshell document as a separate document 6. added Section 6.3.4 to define the nominal study visit and analysis visit
Draft 2.1	19Nov2018	Hong Wang	1. Clarified the TEAE definition to be consistent with 2nd safety endpoint in the protocol. 2. Corrected the typo of "Miettnen and Nurminen method" to "Miettinen and Nurminen method" 3. Updated the SAS version that will be used to version 9.3 or later.
Final 3.0	27Nov2018	Hong Wang	Removed the appendixes because they are already included in the previous sections of the SAP.
Draft 3.1	08May2019	Hong Wang	1. Removed the analysis for AESI because no Adverse Events of Special Interest was identified by the Sponsor 2. Added subgroup analysis by country/region for the assessment of consistency in treatment effects across countries/regions 3. Provided details how the immunogenicity data will be used to define seroprotection and how the upper limit value will be used as continuous variables 4. Added analysis for all AEs occurred from the date of first vaccination through the date of end study

Version	Version Date	Author	Summary of Changes Made
			5. Clarified that the plan for exploratory analyses of antibody responses against Pre-S1 and Pre-S2 and cell-mediated immunity directed against HBs data collected during this study will be detailed in a separate SAP and is outside the scope of this SAP.
Final 4.0	13May2019	Hong Wang	Final version

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.

Dr. Francisco Diaz-Mitoma	May 14, 2019 **Date (DD Mmm YY)**
Chief Medical Officer	
Dr. Vlad Popovic	14 May 2019 **Date (DD Mmm YY)**
VP, Clinical Development and Medical Affairs	
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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:

Hong Wang	**Date (DD Mmm YY)**
Principal Biostatistician	

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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
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
ITT	Intent-to-Treat
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
SSA	Sub-study Analysis Set
SOC	System Organ Class
SPR	Seroprotection rate
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
TLF	Tables, Listings and Figures
VBI	VBI Vaccines Inc
WHO-DD	World Health Organisation - 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 plan for exploratory analyses of antibody responses against Pre-S1 and Pre-S2 and cell-mediated immunity directed against HBs data collected during this study will be detailed in a separate SAP and is outside the scope of this SAP. These analyses will be reported as an addendum to the main Clinical Study Report (CSR).

The analyses described are based on CSP V2.0, dated, 17/Jul/2017.The SAP will be finalized prior to database lock 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 lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in the clinical study report.

1. STUDY OBJECTIVES

1.1 Co-Primary Objectives

- To demonstrate that the seroprotection rate (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 the three-dose regimen of Engerix-B® in adults ≥18 years of age i.e. the lower bound of the 95% two-sided confidence interval (CI) of the difference between the SPR in the Sci-B-Vac™ arm minus the SPR in the Engerix-B® arm, achieved 4 weeks after receiving the third vaccination, will be > - 5%

and

- To demonstrate that the SPR 4 weeks after completion of the three-dose regimen of Sci-B-Vac™ is superior to the SPR 4 weeks after completion of the three-dose regimen of Engerix-B® in older adults ≥45 years of age i.e. the lower bound of the 95% two-sided CI of the difference between the SPR in the Sci-B-Vac™ arm minus the SPR in the Engerix-B® arm, achieved 4 weeks after receiving the third vaccination, will be > 5%.

1.2 Secondary Objectives

- To determine whether the SPR after receiving 2 vaccinations of Sci-B-Vac™, evaluated at 4 weeks and 20 weeks after receiving 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®
- To compare the safety and reactogenicity of Sci-B-Vac™ and Engerix-B®.

1.3 Exploratory Objectives

- To compare the geometric mean concentration (GMC) of anti-HBs 4 weeks after receiving the first vaccination, the second vaccination and the third vaccination, 20 weeks after receiving the second vaccination (just prior to receiving the third vaccination), and 24 weeks after receiving the third vaccination, of Sci-B-Vac™ or Engerix-B®.
- To compare the SPR observed 4 weeks after receiving the first vaccination and second vaccination, 20 weeks after receiving the second vaccination (just prior to receiving the third vaccination), and 24 weeks after receiving the third vaccination, of Sci-B-Vac™ or Engerix-B® on Study Days 28, 56, 168 and 336.
- To compare the proportion of subjects who achieve anti-HBs levels ≥ 100 mIU/mL, as a measure of an especially robust immune response, 4 weeks after each vaccination with either Sci-B-Vac™ or Engerix-B®, on Study Days 28, 56, and 196, and on Study Days 168 and 336.
- To compare the rate of non-response 4 weeks after receiving the third vaccination with Sci-B-Vac™ or Engerix-B®.
- To assess the antibody responses against Pre-S1 and Pre-S2 at baseline, 4 weeks after each injection with Sci-B-Vac™ or Engerix-B® and on Study Days 168 and 336.
- To compare SPR, GMC and rate of non-response in subgroups of interest (e.g. BMI>30) 4 weeks after receiving the third vaccination with Sci-B-Vac™ or Engerix-B®.
- To compare clinical laboratory parameters relative to baseline 1 week after each vaccination with Sci-B-Vac™or Engerix-B® in a subset of subjects (at least 10% of the total number of subjects enrolled to the trial).
- To compare the boost, relative to baseline, of cell-mediated immune response against HBs, 1 week after receiving each vaccination with either Sci-B-Vac™ or Engerix-B® (in a small subset of subjects recruited to an optional sub study at select sites (~50-75 subjects/treatment arm)).

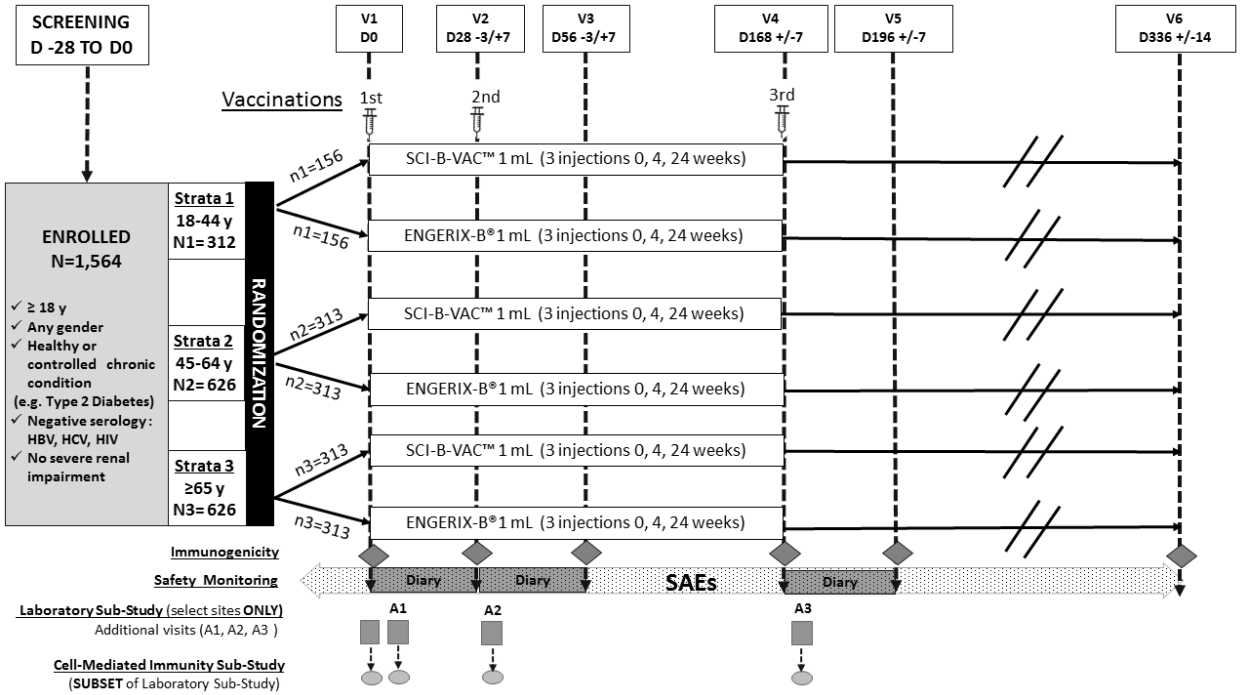
2. STUDY DESIGN

This is a double-blind randomized controlled trial designed to establish the non-inferiority of Sci-B-Vac™ compared to Engerix-B® in adults ≥18 years old. Study subjects will be randomized 1:1 via a web-based system to receive either a total of 3 injections of Sci-B-Vac™ or 3 injections of Engerix-B® intra-muscularly (IM) (one injection on Study Day 0, one injection at 4 weeks (Study Day 28) and one injection at 24 weeks (Study Day 168)), and followed for 24 weeks after receiving the third vaccination.

Randomization will be stratified by study center, and age (18-44 years, 45-64 years and ≥ 65 years). The study subjects, the study center staff performing outcome measurement, and the sponsor will be blinded to vaccine allocation. Study vaccines will be administered by qualified unblinded study center staff.

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

The study population will consist of approximately 1,564 subjects, age ≥ 18 years old, in up to 30 study centers in Europe, Canada, and the U.S individuals of any gender, race and ethnic groups meeting all the inclusion criteria and none of the exclusion criteria.

Inclusion criteria

Subjects must meet all the following criteria:

1. Any gender
2. Age ≥ 18 years
3. In stable health as determined by a physical examination and laboratory tests values. Common chronic conditions such as, but not limited to, type 2 diabetes, high blood pressure, COPD and asthma will be accepted if the condition is well controlled, as determined by the investigator, and not meeting the exclusion criteria. For subjects > 65 years old, Frailty Index ≤3 (see protocol Appendix 1).
4. If female: a) either is 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 a prednisolone-equivalent dose > 20 mg /day (Inhaled and topical steroids are allowed)
3. Known 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) OR

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

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 week prior to enrollment.

4. STATISTICAL BASIS FOR SAMPLE SIZE

The overall sample size for the study is driven by the superiority co-primary analysis in study subjects ≥ 45 years old. Assuming an SPR of 0.81 for Engerix-B® and 0.96 for Sci-B-Vac™, a minimum of 540 subjects (270 per treatment group) provides 90% power to demonstrate superiority of SPR, assuming a 5% margin with a two-sided type 1 error of 0.05, i.e., to rule out a <5% difference in SPR based on the lower limit of the two-sided 95% confidence interval. Based on a targeted enrollment of 80% of study subjects age ≥ 45 years old, an additional 180 (20%) 18-44 years old study subjects would be required, for a total of at least 680 subjects in the full study. A sample size of 680 would provide ≥ 90% power to demonstrate non-inferiority with a 5% margin if the Sci-B-Vac™ SPR is as low as 0.88, with the same SPR for Engerix-B® (0.81), and the two-sided alpha is 0.05. A 5% margin of non-inferiority is justified by the > 90% SPR of Engerix-B® in young adults. In older adults, a 5% margin of superiority represents a clinically meaningful improvement at both the individual level and from a public health perspective, given the reduced immunogenicity of Engerix-B® in this population.

Given the desire to have robust immunogenicity estimates of SPR in the adult population following a three-dose regimen of Sci-B-Vac™ and to guard against a better than expected SPR for Engerix-B® (up to 84% in subjects ≥45 years old), a total of 1,564 subjects will be enrolled to the trial. There will be targeted enrollment, with 80% (~n=1252) of the study population being ≥ 45 years old and 20% (~n=312) being 18-44 years old. This sample size will provide >90% power to establish the superiority of Sci-B-

Vac™ over Engerix-B® in older adults (≥ 45 years old) and non-inferiority in adults ≥ 18 years of age, given the above statistical parameters.

Given the desire to have good representation across the spectrum of older adults, the targeted enrollment of adults ≥ 45 years of age (80%) will be divided equally between the 45-64 years old and ≥ 65 years old strata.

Targeted enrollment by age strata will be as follows:

Age 18-44 years (20%): 312 (~ 156 per arm)

Age 45-64 years (40%): 626 (~313 per arm)

Age ≥ 65 years (40%): 626 (~313 per arm)

Enrollment within each stratum will be stopped once the target has been met.

5. RANDOMIZATION

This is a double blind 2-arm study. A statistician who is not involved in the clinical aspects of the study will generate a permuted blocked randomization list for each site and inside each site for each of the 3 following strata: 18-44 years, 45-64 years and ≥ 65 years old at the date of enrolment. Randomization will be via a web-based IWRS. The site pharmacy and/or unblinded study center staff will receive a notification of the randomization and the treatment allocation for the subject, which should be filed in a locked area/ computer folder not accessed by blinded study center staff. The IWRS will track and supply appropriate medication to the study subjects.

Randomization within an age stratum will stop after the target sample size has been reached.

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 vaccine different from the one assigned at randomization.
- Subjects vaccinated with the correct vaccine but containing a lower volume.

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	V1	Phone Safety Follow-up	V2	Phone Safety Follow-up	V3 (i)	V4	Phone Safety Follow-up	V5 (j)	V6 End of Study Visit
Timelines (days)	-28	0		28		56	168		196	336(a)
Range (days)	-28 to 0		V1 + 5-9	-3/+7	V2 + 5-9	-3/+7	+/-7	V4 + 5-9	+/-7	+/-14
Screening										
Informed Consent	X									
Inclusion & Exclusion Criteria	X									
Physical Examination (b)	X	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			
Blood tests: CBC, liver and renal function, HbA1C if indicated	X									
Urinalysis	X									
Randomization		X								
Vaccination		X		X			X			
Immunogenicity										
Anti-HBs		X(c)		X(c)		X	X(c)		X	X
Anti pre-S1, anti pre-S2		X(c)		X(c)		X	X(c)		X	X
Safety Assessments										
Vital signs	X	X(d)		X(d)			X(d)			
Subject instructed to complete diary		X	X	X	X		X	X		
Recording Local & Systemic Reactions		X	X(e)	X	X(e)		X	X(e)		
Recording Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Unsolicited AEs	X	X	X(g)	X(g)	X(g)	X(f)	X(g)	X(g)	X(g)	X(f)
SAEs, medically significant event, NOCI (h)	Continuous									
Sub-Studies (only at select sites)			A1*		A2*			A3*		
Serum chemistry, Hematology		X(c)	x(k)		x(k)			x(k)		
Cell-mediated immunity		X(c)	x(k)		x(k)			x(k)		

	(a) Or earlier in case of withdrawal (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 at V1, V2 & V4 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 1 week after each vaccination to inquire about reaction to vaccine. 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) V3 should be scheduled at least 3 weeks after V2 (j) V5 should be scheduled at least 3 weeks after V4 (k) 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. A small subset of subjects participating in the clinical laboratory sub-study will be eligible to participate in an optional sub-study on cell-mediated immunity.

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 initial upper limit of quantification (recorded as ">UQ") will be set to that upper limit (UQ). Samples which initially report ">UQ" will be further manually diluted and tested. These manually diluted and tested sample values will be reported in the listings only.

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 results will be calculated. Seroprotection will be determined as follows: if the average of initial and repeat results is ≥10 mIU/mL, then it will be considered seroprotected. If it is less than 10 mIU/mL, then it 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, K, 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 "treated" (i.e., according to the 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 Set (PPS)

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 sero-negative 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 PPS 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 attended study visits outside of the following windows:
    - V2/Day 28 (- 7 / +14 days)
    - V3/Day 56 (-7/+14 days)
    - V4/Day 168 (+/-28 days)
    - V5/Day 196 (-7 / +14 days)

- subjects who developed withdrawal criteria but were not withdrawn
- subjects who received a prohibited concomitant medication [as per exclusion criteria], if the medication and the timing of its administration is considered to have a significant impact on the reliability of subject immunogenicity result
- subjects with a deviation identified through monitoring visits or otherwise, where the deviation is judged to impact the reliability of subject immunogenicity results

In case of vaccination error, subjects in the PPS will be analyzed "as randomized" and the subject who received the wrong vaccination will be excluded from the PPS. 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 the PPS.

If a subject is unblinded during the study, except for suspected unexpected serious adverse reaction (SUSAR), he/she may be excluded from the PPS 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)

6.2.6.1 Clinical Laboratory Sub-study Analysis Set (SSA 1)

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.

6.2.6.2 Sub-study Analysis Set for Cell-mediated Immunity directed against HBs (SSA 2)

All subjects in the All Enrolled Set who actually receive at least one dose of study vaccination and participated in optional sub-study of cell-mediated immunity directed against HBs.

6.2.7 Sub-groups

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

- Age group: (18 – 44 years old vs 45 – 64 years old vs >= 65 years old)
- Age category: (18 – 39 years old vs 40 – 49 years old vs 50 – 59 years old vs 60 – 69 years old vs >= 70 years old)
- Gender (male vs female)
- BMI (<=30 vs >30)
- Smoking Status (current vs past vs non-smoker)

- Diabetes (Diabetic vs non-diabetic)
- Daily alcohol consumption (≥ 4 drinks/day vs 2-3 drinks/day vs 0-1 drink/day)
- Non-study licensed vaccines (no vaccination vs vaccination): Any concomitant vaccines received during the study
- 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 treatment group 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

Laboratory data, vital sign data and physical examination 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 56	57
Visit 4	Day 168	169
Visit A3	Day 175	176
Visit 5	Day 196	197
Visit 6	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 the co-primary 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 the PPS 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	Measurements ≥ 900 mm or Measurements < 0 mm
Induration	Measurements ≥ 500 mm or Measurements < 0 mm

6.3.8 Subject Disposition

The following subject data will be presented by treatment group and overall:

- The number of subjects screened
- The number of screen failures with a breakdown of reasons for screen failure
- 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 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 randomized 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, PPS, Safety Set and SSA1. All demographic and baseline characteristics will be listed and summarized overall and by 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 treatment group and overall. Medical history data will be tabulated for the ITT, FAS, PPS, 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 overall and by 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 will be summarized by treatment group for safety population.

Vaccine administration information will also be listed.

6.3.13 Immunogenicity

The co-primary analyses of the immunogenicity data will be based on the PPS and FAS. Sensitivity analyses using the same approach will be conducted using the ITT. These analyses will be reported both with and without patients in the FAS or ITT 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 treatment group. The following descriptive statistics will be presented for serum concentrations obtained at each nominal time point: n, geometric mean, geometric SD, median, minimum and maximum values.

Individual serum concentration versus actual times will be plotted by treatment group for anti-HBs antibody in linear and semi-logarithmic scale. The geometric mean serum concentrations with

corresponding 95% confidence intervals versus nominal times will also be presented. The bar plot of SPR by treatment on Days 28, 56 and 196 will also be produced based on PPS for all age groups and for age >= 45 years old. All treatment groups will be overlaid on the same plot.

6.3.13.1 Co-Primary Hypotheses

The two co-primary analyses will be tested in sequence, the test for superiority in the subgroup (≥ 45 years old) can only be conducted after non-inferiority in the overall population (≥ 18 years old) has already been shown.

1. Non-Inferiority of Sci-B-Vac™ compared to Engerix-B® will be assessed using the PPS for the entire study population (i.e., adults ≥ 18 years old). The non-inferiority margin is set at 5%. The null and alternative hypotheses are as follows:

Null Hypothesis: SPR(Sci-B-Vac™) –SPR(Engerix-B®) <= -5%

Alternative Hypothesis: SPR(Sci-B-Vac™) –SPR(Engerix-B®) > -5%

Non-inferiority will be assessed using the lower bound of the two-sided 95% confidence interval. If the lower bound is greater than -5%, Sci-B-Vac™ will be declared non-inferior to Engerix-B®, and the study will be considered a success.

2. Superiority of Sci-B-Vac™ compared to Engerix-B® will be assessed using the FAS for the study population of adults ≥ 45 years old who are sero-negative at baseline. In older adults, a 5% margin of superiority represents a clinically meaningful improvement at both the individual level and from a public health perspective, given the reduced immunogenicity of Engerix-B® in this population. Therefore a superiority margin is set at 5%. The null and alternative hypotheses are as follows:

Null Hypothesis: SPR(Sci-B-Vac™) –SPR(Engerix-B®) <= 5%

Alternative Hypothesis: SPR(Sci-B-Vac™) –SPR(Engerix-B®) > 5%

Superiority will be assessed using the lower bound of the two-sided 95% confidence interval. If the lower bound is greater than 0%, Sci-B-Vac™ will be declared statistically superior to Engerix-B®. If the lower bound is greater than 5%, Sci-B-Vac™ will be declared clinically superior to Engerix-B®, and the study will be considered a success.

6.3.13.2 Statistical Methods for Co-Primary Immunogenicity Analyses

<u>Seroprotection rate (SPR) 4 weeks after the third injection</u>

For the primary endpoint of SPR at day 196, 4 weeks following the third vaccination, data from all centers will be pooled for the primary analysis. The estimated 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®.

Upon demonstrating non-inferiority in the overall population (≥ 18 years old), the test for superiority in the subgroup (≥ 45 years old) can be conducted. If the lower bound is greater than 0%, Sci-B-Vac™ will be declared statistically superior to Engerix-B®. If the lower bound is greater than 5%, Sci-B-Vac™ will be declared clinically superior to Engerix-B®.

Sensitivity analyses using the same approach outlined above will be conducted using the FAS for the non-inferiority co-primary analysis. These analyses will be reported both with and without patients in the FAS who are seropositive at baseline. Sensitivity analyses using the ITT analysis set will be conducted for the superiority co-primary analysis. 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. Additional sensitivity analyses will be conducted using a Logistic Regression model, to adjust for age group. Factors for treatment and age group will be included in the model.

- Sample SAS code for the analysis of binary data using logistic regression:

```
PROC LOGISTIC; * specify and sub-select data set as applicable;
     CLASS trt agegrp;
     MODEL seroprotection = trt + agegrp * numerical 0/1-scores identify 'event';
     LSMEANS trt /diff;
     ODS OUTPUT lsmeans=lsmeans diffs=diffs;
RUN;
```

where seroprotection represent the seropositive event, trt represents treatment group and agegrp represents age group (18 - 44 years, 45 - 64 years, >=65 years).

The estimated proportion of responders (i.e., estimated responder rate) and the difference in the proportion of responders between Sci-B-Vac™ and Engerix-B® will be estimated, as well as the 2-sided 95% CIs for the difference. The creation of the estimates of the proportions and difference in proportions will be completed using the process detailed below:

1. Use the logistic regression model to calculate:

   a) Least squares mean estimates of the log odds of Sci-B-Vac™ (Gc) and Engerix-B® (Gp), as well as their corresponding standard errors (S_C and S_P, respectively)

   b) Standard error of the least squares mean estimate of the log odds ratio (S_R)

2. Compute estimates for predicted proportions using the following transformations:

   $P_C = \exp(G_C)/(1 + \exp(G_C))$

   $P_P = \exp(G_P)/(1 + \exp(G_P))$

The difference in proportions is then given by:

$D = P_C - P_P$

3. Estimate the standard error of D by:

   $S_D = \text{sqrt}[P_C^2 (1-P_C)^2 S_C^2 + P_P^2 (1-P_P)^2 S_P^2 + P_C (1-P_C) P_P (1-P_P) S_R^2 - P_C (1-P_C) P_P (1-P_P) (S_C^2 + S_P^2)]$

Analyses of the co-primary endpoints will also be conducted and reported by key sub-groups using the sub-groups identified in Section 6.2.7.

- Sample SAS code for the subgroup analysis of binary data:

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

where seroprotection represent the seropositive event, trt represents treatment group and subgroup represents subgroup defined in Section 6.2.7.

6.3.13.3 Statistical Methods for Secondary Objective Analyses

If the co-primary hypotheses are significant, the following secondary hypotheses will be tested in the following pre-specified order, with each hypothesis using a two-sided 5% significance level. If an endpoint fails to reach statistical significance, following hypothesis tests will not be performed.

1) Non-Inferiority of Sci-B-Vac™, 20 weeks following the second vaccination, compared to Engerix-B®, 4 weeks following the third vaccination, will be assessed using the PPS for the entire study population (i.e., adults ≥ 18 years old). The non-inferiority margin is set at 5%. The null and alternative hypotheses are as follows;

Null Hypothesis: SPR(Sci-B-Vac™) –SPR(Engerix-B®) <= -5%

Alternative Hypothesis: SPR(Sci-B-Vac™) –SPR(Engerix-B®) > -5%

Non-inferiority will be assessed using the lower bound of the two-sided 95% confidence interval. If the lower bound is greater than -5%, Sci-B-Vac™ 20 weeks following the second vaccination will be declared non-inferior to Engerix-B® 4 weeks following the third vaccination, and the next secondary hypothesis will be tested.

2) Non-Inferiority of Sci-B-Vac™ 4 weeks following the second vaccination compared to Engerix-B® 4 weeks following the third vaccination will be assessed using the PPS for the entire study population (i.e., adults ≥ 18 years old). The non-inferiority margin is set at 5%. The null and alternative hypotheses are as follows;

Null Hypothesis: SPR(Sci-B-Vac™) –SPR(Engerix-B®) <= -5%

Alternative Hypothesis: SPR(Sci-B-Vac™) –SPR(Engerix-B®) > -5%

Non-inferiority will be assessed using the lower bound of the two-sided 95% confidence interval. If the lower bound is greater than -5%, Sci-B-Vac™ 4 weeks following the second vaccination will be declared non-inferior to Engerix-B® 4 weeks following the third vaccination.

The analysis for secondary endpoints will be conducted the same approach using the PPS for the non-inferiority co-primary analysis (Section 6.3.13.2). The estimated proportions and two-sided 95% CIs for Engerix-B® at Day 196 and Sci-B-Vac™ at Day 56 or Sci-B-Vac™ at Day 168 as well as the difference in proportions between Engerix-B® and Sci-B-Vac™ [SPR(Sci-B-Vac™) – SPR(Engerix-B®)] and two-sided 95% Miettinen-Nurminen CIs will be calculated and reported. Funnel plot will be produced to investigate the impact of center.

Sensitivity analyses using the same approach outlined above will be conducted using the FAS for both secondary analyses. These analyses will be reported both with and without patients in the FAS who are seropositive at baseline. Additional sensitivity analyses will be conducted using a Logistic Regression model, to adjust for age group. Factors for treatment and age group will be included in the model.

Analyses of the above secondary endpoints will also be conducted and reported by key sub-groups using the sub-groups identified in Section 6.2.7.

6.3.13.4 Exploratory Objective Analyses

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

Geometric mean concentration (GMC)

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

Adjusted estimates of GMCs and their associated 95% CIs at Day 28, Day 56, Day 168, Day 196 and Day 336 will each be determined using an analysis of covariance (ANCOVA) model with factors for treatment, age group, and a covariate for the log transformed pre-vaccination (baseline) titer. Antibody 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 difference in GMCs between the two treatment groups, and associated two-sided 95% CIs will also be presented. Imputation methods will not be used.

The above analyses will be conducted and reported for all subjects age ≥ 18 years old and for subjects age ≥ 45 years old. Analyses of GMC in both age cohorts will also be reported by sub-group using the sub-groups identified in Section 6.2.7. Sub-group analyses will include additional factors in the model, a factor for the sub-group of interest and the interaction between the sub-group and treatment.

Sample SAS code for ANCOVA model:

```
        PROC MIXED;
        CLASS treatment agegrp;
        MODEL log(var) = treatment agegrp log(baseline of var);
/* var = anti-HB titer GMC */
                LSMEANS treatment / DIFF CL ALPHA=0.05;
                ODS OUTPUT LSMEANS=ls_means Diffs=diff;
QUIT;
        RUN;
```

Sample SAS code for ANCOVA model for sub-group analyses:

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

where var represent the anti-HBs titer, treatment represents treatment group, agegrp represents age group (18 - 44 years, 45 - 64 years, >=65 years) and subgroup represents subgroup defined in Section 6.2.7.

Binary data (e.g. proportion of subjects with anti-HBs levels ≥ 100mIU/mL and proportions of subjects achieving seroprotection, please see Section 1.3 for all binary data interested) will be summarized using frequency counts and percentages, by time point. Data from all centers will be pooled for these analyses. The difference in proportions and two-sided 95% CIs, calculated using the Miettinen and Nurminen

method, will be reported. Additional sensitivity analyses will be conducted using a Logistic Regression model, to adjust for age group. Factors for treatment and age group will be included in the model.

- Sample SAS code for the analysis of binary data:

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

- Sample SAS code for the analysis of binary data using logistic regression:

```
PROC LOGISTIC; * specify and sub-select data set as applicable;
     CLASS trt agegrp;
     MODEL seroprotection = trt + agegrp * numerical 0/1-scores identify 'event';
     LSMEANS trt /diff;
     OUTPUT lsmeans=lsmeans diffs=diffs;
RUN;
```

- Sample SAS code for the subgroup analysis of binary data:

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

where seroprotection represent the binary event, trt represents treatment group, agegrp represents age group (18 - 44 years, 45 - 64 years, >=65 years) and subgroup represents subgroup defined in Section 6.2.7.

The above analyses will be conducted and reported for all subjects ≥ 18 years old and for subjects ≥ 45 years old. Analyses of binary data in both age cohorts will also be reported by sub-group using the sub-groups identified in Section 6.2.7.

6.3.14 Safety Analysis

Analysis for laboratory variables will be based on SSA 1. The analysis of the rest of safety variables will be based on the Safety Set.

6.3.14.1 Completer Analysis on 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 3.

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	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization

		> 24 hours or interferes with activity		
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 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
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 AE will be presented by treatment group for each symptom overall, and by treatment group and severity for each age group 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
- Adverse events 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, chemistry) 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/hematology from baseline will only be calculated in the clinical laboratory sub-study analysis set (SSA 1). In addition, absolute and change from baseline values will be categorized according to the toxicity scales (See protocol Appendix 4 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 © 2002-2003. 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 2.0

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