TITLE:

A Double-blind Randomized **Con**trolled Trial to A**s**sess the Lo**t**-to-lot Consistency of Sci-B-V**a**c™ i**n** Adul**t**s **(CONSTANT)**

Protocol Identifying Number:

Sci-B-Vac–002

EudraCT Number: 2017-001820-22

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Amendment 3

Date of version**:**

May 09, 2018

Study Sponsor:

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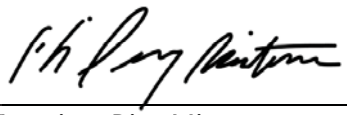
Confidentiality Statement

Sponsor Signature Page

Sponsor Signatory:



09/05/2018

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List of abbreviations

aa: amino acid
Ab: antibody
AE: adverse event
$Al(OH)_3$: aluminum hydroxide
$AlPO_4$: aluminum phosphate
ALT: alanine transaminase
Anti-HBc: hepatitis B core antibody
Anti-HBs: hepatitis B surface antibody
AP: alkaline phosphatase
AST: aspartate transaminase
BMI: body mass index
bp: base pair
BUN: Blood Urea Nitrogen
CBC: complete blood count
CG: Cockcroft-Gault
CHO: Chinese hamster ovary cell
CI: confidence interval
CMP: clinical monitoring plan
CPK: creatine phosphokinase
CRO: contract research organization
CVID: common variable immune deficiency
DBP: diastolic blood pressure
dL: deciliter
DNA: deoxyribonucleic acid.
DMC: data monitoring committee
EEA: European economic area
EPO: erythropoietin
E.U.: European Union
FDA: Food and Drug Administration
FIMEA: Finish Medicine Agency
g: gram
GCP: Good Clinical Practice
GGT: gamma-glutamyl transferase
GMC: geometric mean concentration
GMCSF: Granulocyte macrophage colony-stimulating factor
GMP: Good Manufacturing Practice
HBsAg: hepatitis B surface antigen
HBV: hepatitis B virus
HCT: hematocrit
HCV: hepatitis C virus
HIV: human immunodeficiency virus
ICH: International Conference on Harmonization
IEC: independent ethics committee
IM: intramuscular
IRB: institutional review board
IWRS: interactive web response system
LLN: lower limit of normal range
MCH: mean cell hemoglobin
MCHC: mean cell hemoglobin concentration
MCV: mean corpuscular volume
MedDRA: medical dictionary for regulatory activities
mEq: milliequivalent
mg: milligram
mIU: milli-international unit
mm: millimeter
mL: milliliter
µg: microgram
PT: prothrombin time
SAE: serious adverse event
SBP: systolic blood pressure
SOP: standard operating procedure
SPR: seroprotection rate
SUSAR: suspected unexpected serious adverse reactions
SVR: sustained virologic response
ULN: upper limit of normal range
U.S.: United states
VBI: VBI Vaccines Inc
WBC: white blood cells count

Statement of Compliance

By signing below, the Principal Investigator agrees to adhere to the protocol. Any change in the study must be reviewed by a formal protocol amendment procedure and the Principal Investigator will submit all changes, amendments and revisions to all relevant ethical review bodies as defined in section 13 of this protocol. Any change to the protocol that affects subject selection, safety, or changes in the conduct of the trial will require written approval from all relevant ethical review bodies before implementing the change.

The Principal Investigator also agrees to conduct the study in accordance with:

- All applicable Laws and Regulations
- the International Conference on Harmonization guidelines on Good Clinical Practice (ICH GCP), copies of which have been provided to the principal investigator.

The Principal Investigator also thereby agrees that the relevant ethical review body will approve all subject informed consent form templates before the study is initiated. The investigator will obtain informed consent and document this process for all subjects enrolled in this study.

Principal Investigator	Signature	Date (dd/mmm/yyyy)

PROTOCOL SUMMARY

Title	A Double-blind Randomized Controlled Trial to Assess the Lot-to-lot Consistency of Sci-B-Vac™ in Adults
Clinical Trial Phase	3
Study sponsor	VBI Vaccines Inc.
Number of sites	30-40 sites (Canada, Europe, United States)
Background & Rationale	Hepatitis B virus (HBV) is a human double-stranded enveloped DNA virus that causes an acute infection that, in some cases, may develop into a chronic disease. Approximately 260 million people are chronically infected by the hepatitis B virus (HBV) worldwide[1]. In 2013, it is estimated that 686,000 people of all ages died from complications of hepatitis B, such as liver cirrhosis and liver cancer[2]. The progressive implementation of universal immunization programs in infants, children, and adolescents in a total of 184 countries[1] has resulted in vaccine coverage of 82% of children and a drop in the incidence of hepatitis B in these countries. However, adults remain at risk of becoming infected with HBV. For instance, according to the European Centre for Disease Prevention and Control, the most affected age group for both acute and chronic infections was the group of 25–34-year-olds, accounting for 33.8% of the 22,442 cases reported in 2014 by the 30 EU/EEA Member States[3]. Monovalent HBV vaccines licensed in the European Union (E.U.), the United States (U.S.) and Canada, such as Engerix-B®, are second-generation vaccines using recombinant DNA technology to express the HBV DNA sequence coding for the small hepatitis B surface antigen (HBsAg) in yeasts. For Engerix-B®, the 1 mL dose containing 20 µg of HBsAg is the formulation approved for the immunization of healthy adults. In adults, the most commonly recommended immunization schedule consists of three injections of vaccine, two injections 4 weeks apart, followed by a third injection 24 weeks after the initial injection. A serum concentration of hepatitis B surface antibody (anti-HBs) ≥10mIU/mL, 4 weeks after the third injection, is considered protective[4], and is associated with long term immunity to hepatitis B[5]. The seroprotection rate (SPR), defined as the percentage of individuals achieving a serum concentration of hepatitis B surface antibody (anti-HBs) ≥10mIU/mL, is accepted as an immunological surrogate of clinical protection against HBV infection. While the SPRs elicited by currently licensed hepatitis B vaccines in children and adolescents are high (≥98%)[6], up to 10% of all adults fail to achieve anti-

	HBs levels ≥10mIU/mL after a three-dose schedule[6], and are considered non-responders to hepatitis B vaccination. The proportion of adult non-responders is even higher in individuals age 30 years and above, where there is a well-documented age-dependent decline in response rate to currently licensed HBV vaccines[7, 8]. In recent phase 3 trials where Engerix-B® was the comparator, the SPR 4 weeks after completion of the three-dose regimen were 74%, 72% and 68%, in adults 40-49, 50-59 and 60-69 years old, respectively[8-10]. Beyond age, other factors are known to be associated with reduced immunogenicity of HBV vaccines, including obesity[11], male gender[12], smoking[12], diabetes[12], and concomitant disease[12]. Moreover, compliance with the primary three-dose schedule is low, with up to 40% of vaccinees missing the third injection, resulting in inadequate clinical protection against HBV infection[13]. A more potent hepatitis B vaccine that is safe, more immunogenic, protects faster and with fewer injections and eliminates the need for re-vaccination therefore has important public health implications. Sci-B-Vac™ is a third-generation hepatitis B vaccine produced in mammalian Chinese hamster ovary (CHO) cells, genetically modified to produce the three HBV envelope proteins. Unlike the second-generation hepatitis B vaccines, which only contain the small S antigen, Sci-B-Vac™ includes the small S, pre-S1 and pre-S2 hepatitis B surface antigens. The putative biological function and incremental significance of the immune response to each of the envelope proteins (i.e., S, pre-S2 and pre-S1) has been described previously[14] with the pre-S antigens expressing highly immunogenic T and B cell epitopes. The latter is an important property of Sci-B-Vac™[15,16] that is believed to account for its heightened immunogenicity, resulting in high SPRs in older individuals following vaccination. Product distribution data globally estimates that over 500,000 infants, children and adults have been vaccinated with Sci-B-Vac™. However, since its original development in 1989, Sci-B-Vac™ has undergone a number of changes in formulation, manufacturer and proprietary name. The sponsor, VBI Vaccines Inc., is proposing two phase III clinical trials to generate additional safety and immunogenicity data for the current adult Sci-B-Vac™ formulation [1 mL, 10 µg HBsAg, aluminum hydroxide ($Al(OH)_3$) adjuvant, without thimerosal] in the adult population prior to seeking licensure in Canada, the U.S. and the E.U. The primary objective of the current study is to verify that the manufacturing equivalence of Sci-B-Vac™ is consistent and 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.
Investigational products	INVESTIGATIONAL PRODUCT Sci-B-Vac™ contains the three viral surface antigen forms: pre-S1, pre-S2, and S. Each single-dose vial (1.0 mL) contains 10 µg of hepatitis B surface antigens adsorbed onto 0.5 mg of aluminum as aluminum hydroxide

	$[Al(OH)_3]$, sodium chloride, potassium chloride, disodium hydrogen phosphate dodecahydrate, potassium dihydrogen phosphate anhydrous and water for injection. Three consecutive lots of Sci-B-Vac™ will be used in this study, each containing 10 µg of hepatitis B surface antigen with aluminum hydroxide as an adjuvant, delivered as a 1.0 mL intramuscular injection: • Group A: Sci-B-Vac™ "Lot A" • Group B: Sci-B-Vac™ "Lot B" • Group C: Sci-B-Vac™ "Lot C" ACTIVE COMPARTOR Engerix-B® (1.0 mL single dose vials), delivered as an intramuscular injection. Each vial contains 20 µg of hepatitis B surface antigen S adsorbed onto 0.5 mg of aluminum as aluminum hydroxide.
Study Design **(see also Figure 1)**	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) with one of three independent consecutive lots of Sci-B-Vac™ or Engerix-B®, according to a three-dose immunization schedule. Study subjects will receive one injection on Study Day 0, one injection at 4 weeks (on Study Day 28) and one injection at 24 weeks (on Study Day 168). Subjects will be followed for 24 weeks after the third injection. Randomization will be stratified by study center. The 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. Upon confirmation of enrollment, each subject will be asked to come for a total of 5 visits (noted V1, V2, V3, V4, and end of study visit, V5). Subjects will be followed a minimum of 48 weeks after the first injection on Study Day 0, with at least 24 weeks of follow-up safety assessments after the third injection. Immunization will consist of three single dose vaccinations with one of three different Sci-B-Vac™ lots or Engerix-B® injected intramuscularly (IM) in the deltoid muscle at 0, 4 weeks (on Study Day 28), and 24 weeks (on Study Day 168), as per the current recommended HBV immunization schedule in adults. Subjects will remain in the clinic at least 30 minutes after each vaccination to be observed for rare adverse reactions. There will be a safety follow-up by telephone 7 days after each vaccination to inquire about local and systemic reactions. Based on these follow up

	assessments, subjects may be asked to come for supplemental visits for clinical assessment if warranted. In addition, the study center will also contact the subject by telephone 4 weeks after the second vaccination to assess the subject's status. Immunogenicity will be assessed at baseline (Study Day 0) and on Study Days 168, 196 and 336. A validated quantitative hepatitis B surface antibody [anti-HBs] will be used (see below primary endpoint). Safety evaluations will include standardized methods for local and systemic vaccine reactions, repeated vital signs and physical examinations, 48 week follow-up for serious adverse events (SAE), medically significant events or new onset of chronic illness (at least 24 weeks after the third dose of vaccine), and changes in concomitant medication. At select sites, subjects will be asked to come for 3 additional visits (denoted A1, A2, A3) to assess clinical laboratory parameters (hematology, biochemistry) one week after each vaccination (Study Days 7, 35 and 175), as part of a clinical laboratory sub-study. The clinical laboratory sub-study will include at least 10% of the total number of subjects enrolled to the trial. The total study duration for each subject (assuming a screening period of 28 days or 4 weeks) is 364 days or 52 weeks.
Intervention Description	Each subject will receive a total of 3 injections of Sci-B-Vac™ or 3 injections of Engerix-B® in the deltoid muscle: one injection of 1 mL on Study Day 0, one injection of 1 mL at 4 weeks (on Study Day 28), and one injection of 1 mL at 24 weeks (on Study Day 168) as per the current recommended HBV immunization schedule in adults. All injections will be done intramuscularly (IM).
Sample Size	3,200 subjects (800 subjects per study arm)
Study Population:	Adults 18-45 years old, meeting all the inclusion criteria and none of the exclusion criteria below. **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 is not of childbearing potential, defined as postmenopausal (12 months with no menses without an alternative medical cause)

	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 **Exclusion criteria** Subjects meeting any of the following 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. 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, autommune 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 week prior to enrolment. 7. Has received blood products or immunoglobulin within 90 days of enrollment or is likely to require blood products during the study period. 8. Subject in another clinical trial with an investigational drug or a biologic within 30 days of enrollment. 9. Has received granulocyte-macrophage colony stimulating factor (G/GM-CSF) or erythropoietin (EPO) within 30 days of enrollment or likely to require GM-CSF or erythropoietin during the study period. 10. Any history of cancer requiring chemotherapy or radiation within 5 years of randomization or current disease. Low risk basal cell carcinoma will be accepted (low risk being defined by the following: 1) location on the trunk of the body, arms, legs, cheeks, forehead, temples, scalp, neck or chin and 2) less than 2 cm, and 3) nodular or superficial, and 4) primary cancer that has not come back after treatment and 5) edge of the cancerous area is clear and smooth and 6) not located in or around nerves). 11. Any skin abnormality or tattoo that would limit post-vaccination injection site assessment. 12. History of allergic reactions or anaphylactic reaction to any vaccine component. 13. Unwilling, or unable in the opinion of the investigator, to comply with study requirements, including the use of adequate birth control methods. 14. Immediate family members of study center staff (parents, siblings, children). 15. Current or past hepatitis B infection or prior vaccination as evidenced by HBV markers (anti-HBc, anti-HBs, HBsAg) at screening. 16. Known hepatitis C infection or positive Hepatitis C serology at screening, unless treated and cured (defined as documented sustained

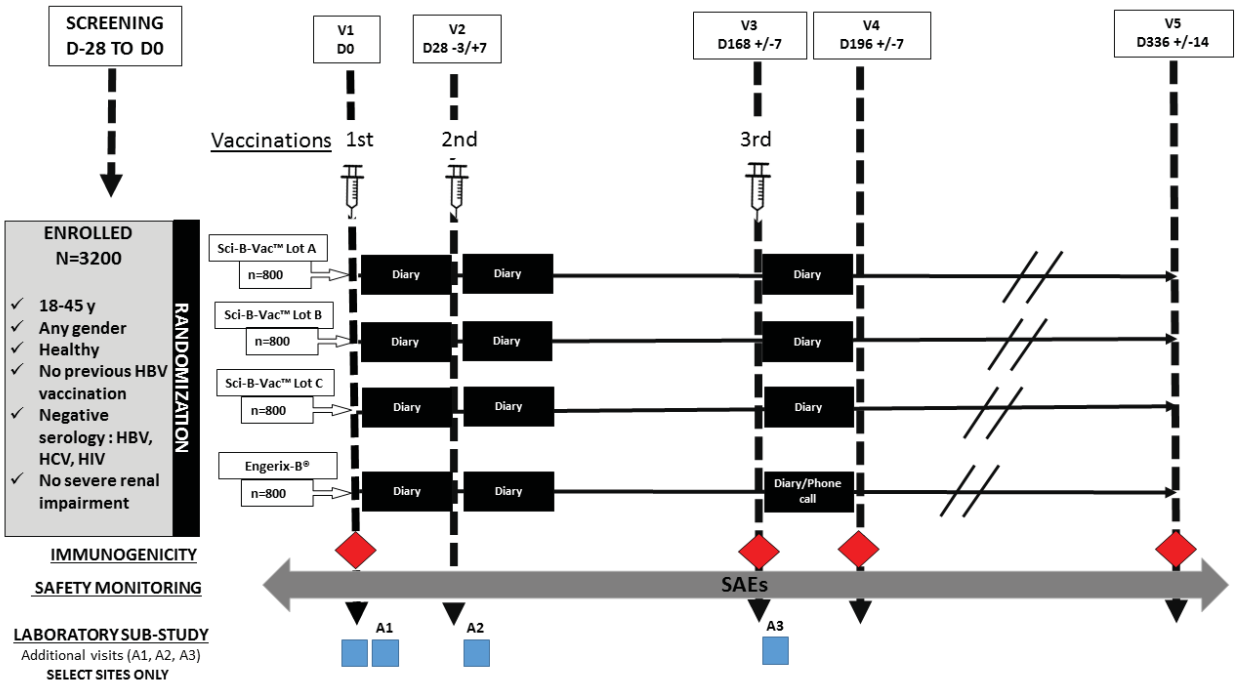
	virologic response (SVR) or negative viral load ≥ 12 weeks after cessation of antiviral therapy). 17. Known human immunodeficiency virus (HIV) infection or positive HIV serology at screening. 18. Renal impairment with Glomerular Filtration Rate (GFR) < 60 mL/min/ 1.73 m^2 at screening. 19. BMI ≥ 35. 20. Uncontrolled hypertension (defined as an average SBP ≥ 150 mmHg or an average DBP ≥ 95 mmHg based on the last three measurements in individuals diagnosed and treated for hypertension, and in people without a diagnosis of hypertension). 21. Diagnosis of Type 1 or Type 2 diabetes or HbA1C ≥ 6.5% at screening. 22. Any laboratory test abnormality that would be considered of Grade 1 severity or above as per FDA guidelines for grading clinical laboratory abnormalities (see Appendix 3 in Protocol) **and** is considered as clinically significant by the investigator. Grade 3 severity or above is exclusionary, regardless of clinical assessment.
Study Duration	~15-18 months (recruitment period + 12 month follow up)
Subject Duration	Subjects will be followed a minimum of 48 weeks after the first vaccination on Study Day 0, with at least 24 weeks of follow-up safety assessments after the third vaccination on Study Day 168.
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 on Study Day 196. This objective will be met if the following condition is satisfied: • The upper and lower bound of the two sided 95% confidence interval (CI) of the geometric mean concentration (GMC) of anti-HBs ratios 4 weeks after the third injection, 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]
Secondary Objectives	**Immunogenicity** To demonstrate that the SPR 4 weeks after completion of the three-dose regiment 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 in the 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®
Exploratory Objectives	• To assesses 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 assesses 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®. Each of the above exploratory objectives will be assessed for each Sci-B-Vac™ lot separately, as well as for the difference between each Sci-B-Vac™ lot. In addition, they will also be assessed for all 3 lots of Sci-B-Vac™ pooled together, for the Engerix-B® group and for the difference between all 3 pooled lots of Sci-B-Vac™ and Engerix-B®.
Immunogenicity Endpoints	• Geometric Mean Concentration (GMC) of anti-HBs in serum after 2 vaccinations, just prior to receiving the third vaccination, and 4 weeks and 24 weeks after the third vaccination with Sci-B-Vac™ or Engerix-B®, on Study Days 168, 196, and 336, respectively. The GMC at Study Day

	196 is the basis for assessing lot-to-lot consistency of the three consecutive lots of Sci-B-Vac™. • Seroprotection rate after 2 vaccinations, just prior to receiving the third vaccination, and 4 weeks and 24 weeks after the third vaccination with Sci-B-Vac™ or Engerix-B®, on Study Days 168, 196, and 336, respectively. Seroprotection is defined as anti-HBs levels ≥ 10mIU/mL in serum. Seroprotection rate (SPR) is the percentage (%) of subjects achieving seroprotection. • Proportion of subjects achieving anti-HBs levels ≥ 100mIU/mL in serum, 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. • 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. • 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®.
Safety endpoints	• Number (%) of subject-reported, solicited (on the day of vaccination and during the next 6 days), number (%) of unsolicited adverse events (AE) (on the day of vaccination and during the next 27 days), and number (%) of SAEs, medically significant event or new onset of chronic illness (through Day 336). Adverse events will be classified by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, severity, seriousness, investigator and Sponsor causality assessment, and time since vaccination. • Number (%) of subjects with abnormal vital signs; physical examination findings, compared to baseline. • Number (%) of subjects with abnormal clinical laboratory parameters from baseline assessments, one week after each vaccination with either Sci-B-Vac™ or Engerix-B® (clinical laboratory sub-study).

SCHEMATIC OF STUDY DESIGN

Figure 1: Schematic of Study Design



PROTOCOL AMENDMENTS Sci-B-Vac-002

Protocol Version	Issue Date
Original Protocol	5 May 2017
Amendment 1	17 July 2017
Amendment 2	04 December 2017
Amendment 3	09 May 2018

Amendment 3 (09 May 2018)

The overall reason for the amendment: The overall reason for the amendment is to reduce the Glomerular Filtration Rate (GFR) threshold to <60 mL/min/1.73 m^2, to allow subjects with mild loss of kidney function to be enrolled to the study.

Applicable Section(s)	Description of Change(s)
Protocol Summary "Exclusion criteria" and Section 4.1.2 "Exclusion criteria" and Section 6.2.2 "Screening laboratory evaluation".	The glomerular Filtration Rate (GFR) threshold for exclusion criteria #18 has been reduced from <90 to <60 mL/min/1.73 m^2.
Rationale: The Glomerular Filtration Rate (GFR) threshold was reduced to <60 mL/min/1.73 m^2, to allow subjects with mild loss of kidney function to be enrolled to the study.	
Section 6.1.3 "Collect Demographic Data" and Section 6.2.2 "Screening laboratory evaluations"	Weight was removed as a factor contributing to the GFR calculation. Race was added as a factor used to calculate GFR.
Rationale: Clarification provided that weight is not used to calculate GFR using the CKD-EPI creatinine equation.	

Amendment 2 (04 December 2017)

The overall reason for the amendment: The overall reason for the amendment is to provide clarification in Section 6.1.9 on which medications are not permitted during the study and to specify in Section 7.1.9 that the reference safety information in the U.S. product insert will be used to establish expectedness of adverse events for the comparator, Engerix-B. Clarification on the collection and storage of laboratory blood samples and re-testing procedures during screening is also provided. Changes are listed in the order in which they appear in the protocol.

Applicable Section(s)	Description of Change(s)
Protocol Summary "Inclusion Criteria" and Section 4.1.1 Inclusion criteria	Postmenopausal is now defined as 12 consecutive months with no menses without an alternative medical cause.
Rationale: To improve clarity.	
Section 6.1.9 "Concomitant medications and intercurrent medical conditions"	Section 6.1.9 has been revised to make it clear that the medications not permitted on study are the same as those listed in the exclusion criteria, and if taken may result in treatment withdrawal (per Section 4.3.2).
Rationale: To improve clarity of treatment withdrawal criteria "received a non-permitted medication" in Section 4.3.2.	
Section 6.2.5 "Biological samples, handling, storage and analysis"	Details of blood storage and procedures for the withdrawal and destruction of samples is now provided.
Rationale: Details and procedures of the storage and destruction of blood samples added to the protocol, for consistency with the informed consent.	
Section 6.2.5 "Biological samples, handling, storage and analysis"	Clarification provided on the provision of a central laboratory manual, detailing the handling, shipping, storage and analysis of blood samples for immunogenicity testing. Screening and safety laboratory samples will be collected, processed and analyzed according to local standard operating procedures.
Rationale: Clarification that a laboratory manual will only be provided for blood samples for centralized immunogenicity testing.	

Section 6.3.1 "Screening"	The re-test procedure during the screening window (-28 Days to 0) is now defined.

Rationale: To improve clarity on when re-testing during screening is permitted, how it should be documented and the approval process.

Section 7.1.9 "Expectedness"	Section 7.1.9 has been revised to include that unexpectedness for Engerix-B will be determined based on reference safety information that appears in the U.S. product insert.

Rationale: To provide clarity on the reference document used to establish the expectedness of adverse events of Engerix-B.

<u>Amendment 1</u> (17 July 2017)

The overall reason for the amendment: The overall reason for the amendment is to change the short-term clinical laboratory follow-up on the entire study population to a more intensive clinical laboratory follow up over the full three-dose regimen on a subset (at least 10%) of the entire study population, and to provide per-protocol clarifications in response to study center inquiries. Changes are listed in the order in which they appear in the protocol.

Applicable Section(s)	**Description of Change(s)**
Cover page and Page Header	Update to version 2.0 from version 1.0 and to update of corresponding date of version. "Amendment 1" and a study acronym have also been added.

Rationale: Change made to reflect the update in the protocol version to Amendment 1 and the addition of a study acronym for study identification.

"Statement of Compliance"	Site signatories now limited to the Principal Investigator. Co-investigators will be required to sign the Delegation of Responsibilities Log on site.

Rationale: Change made to reduce the administrative burden during site qualification.

Protocol Summary "Investigational Product" and Section 5.1.2 Formulation and Labelling"	"10 µg of Hepatitis B surface antigen with aluminum hydroxide ($Al(OH)_3$) as an adjuvant (0.5 mg/mL)" changed to "10 µg of hepatitis B surface antigens adsorbed onto 0.5 mg of aluminum as aluminum hydroxide". Repeated text after each defined Lot (A, B, C) removed for clarity and preceding sentence revised accordingly.

Rationale: Clarification on the amount of aluminum per 1 mL in the aluminum hydroxide adjuvant.

"Protocol Summary" – Study Design	Change made to reflect that clinical laboratory assessments will be carried out in study subset (at least 10% of the study cohort) throughout the full three-dose regimen (clinical laboratory sub-study), instead of on the full study cohort after only one vaccination.

Rationale: Data on a subset (at least 10%) of the total number of subjects enrolled to the trial will provide information sufficient to assess clinical laboratory risks to subjects receiving the entire schedule of Sci-B-Vac™, while reducing the visit burden on the remaining subjects enrolled to the study.

"Protocol Summary" and Section 4.1.2 "Exclusion Criteria" #21, Section 6.2.2 Screening laboratory evaluations , Appendix 1 Schedule of Events	HbA1C added as a screening test and exclusion criteria #21 expanded to include people with an HbA1C ≥ 6.5% at screening.

Rationale: A screening test for HbA1C has been added to the list of screening laboratory tests in order to exclude people from the study with undiagnosed diabetes. People with an HbA1C ≥ 6.5% will not be eligible to participate in the study.

"Protocol Summary" and Section 4.1.2 "Exclusion Criteria" #20	The definition of uncontrolled hypertension (SBP ≥150 mmHg or DBP ≥95 mmHg) has been expanded to people without a diagnosis of hypertension.

Rationale: This change was made to ensure that no subject with higher than grade 1 hypertension is enrolled to the study, for safety reasons.

"Protocol Summary" and Section 2.3 "Exploratory Objectives"	Identifies 100mIU/mL as an important measure of an especially robust immune response to vaccination.

Rationale: This clarification was provided to identify 100mIU/mL as an important measure of an especially robust immune response to vaccination and of long-term immunity, and therefore is an important exploratory objective of the study (and not a typographical error).

"Protocol Summary" and Section 3.3 "Safety Endpoints"	Separate safety endpoint now defined for the number (%) of subjects with abnormal clinical laboratory tests, from clinical laboratory sub-study.

Rationale: This clarification was provided to delineate this endpoint as specific to the clinical laboratory sub-study.

Study Schema	Changes made to the schema to reflect the additional visits required at select sites for the clinical laboratory assessments, as part of a laboratory sub-study. The 7-day V2 visit in the full study cohort has been replaced with a 7-day telephone follow up call and all subsequent visits are now reduced by one (i.e. V3 -> V2) in the main study.

Rationale: Changes made to the schema to reflect that the additional visits and clinical laboratory assessments for the clinical laboratory sub-study are only being done at select sites, thereby reducing the number of study visits by one in the main study.

Section 1.3.1 Sci-B-Vac™ Description	Countries where Sci-B-Vac™ is approved and marketed is now provided.

Rationale: Providing the list of countries where Sci-B-Vac™ is marketed clarifies how product distribution globally has reached 500,000.

Section 3.1 "Study Design"	Changes made to reflect the addition of laboratory sub-study at select sites, with laboratory assessments at Day 0 and 7 days after each vaccination (on Study Day 7, 35 and 175).

Rationale: To improve clarity and consistency within the protocol and to accurately reflect the laboratory safety assessments in the clinical laboratory sub-study.

Sections 3.1, 6.2.4, 6.3.2, 6.3.5, 6.3.6	Antibody levels and characteristics will be measured and compared between Sci-B-Vac™ and Engerix-B®.

Rationale: This modification was made to allow for some mechanistic studies to better characterize the immune responses to Sci-B-Vac™ and Engerix-B®.

Section 3.3 "Safety Endpoints"	Urinalysis removed from the Day 7 list of safety evaluations.

Rationale: Urinalysis removed from the list of evaluations, to be consistent with Appendix 1 Schedule of Events.

Section 3.3 "Safety Endpoints"	Baseline values (Study Day 0) added as a reference for assessing abnormal clinical laboratory tests in the clinical laboratory sub-study.

Rationale: Change from baseline in clinical laboratory values is an important measure of the impact of vaccination on laboratory parameters.

Section 4.3.2 "Subject Withdrawal from Investigational Product"	The use of a concomitant medication not allowed on study as a possible reason for withdrawal from the investigational product (after consultation with the medical monitor) is now provided as an example under "Other (specify)".

Rationale: It is expected that some study subjects may need to be removed from the investigational product because they require a concomitant medication not permitted while on the study.

Section 5.6.1 "Safety follow up and management of reactions"	All subjects must record their daily temperature in their diary. The condition that only subjects with a low grade fever need to record their daily temperature, has been removed.

Rationale: All subjects are required to complete all elements of the safety diary provided at each vaccination, including the daily temperature log.

6.1.2 "Check Inclusion and Exclusion Criteria"	Verification of eligibility against all inclusion and exclusion criteria required prior to randomization. Prior to vaccine administration on Study Days 0, 28, and 168, the investigator or qualified designee must only verify that the subject remains eligible to be administered the vaccine and to remain on the study.

Rationale: Clarification provided that on the days of vaccine administration, subject must only be verified to be eligible to have the vaccine administered (i.e. no fever, no contraindicated medications that would preclude vaccination) and to continue on the study.	
Section 6.1.10 "Recording of adverse events"	Clarification is provided that the recording of solicited pain, tenderness and pruritus at the injection site and oral daily temperature is only required on the day of injection and for 6 days after the injection. The original safety laboratory Visit 2, seven days after the first vaccination, has been replaced in the main study with a follow up telephone call.
Rationale: This clarification is provided to distinguish between solicited adverse events (up to 6 days post injection) and unsolicited adverse events (up to 27 days post injection) and to clarify that a follow-up telephone call will occur 7 days after each vaccination, for consistency with section 3.1.	
Section 6.2.1 "Urine Pregnancy Test"	Clarification is provided that a confirmatory serum pregnancy test is required in the event of a positive urine pregnancy test. If the serum pregnancy test is positive, the subject will be withdrawn from the study (per section 4.3.1). If the serum pregnancy test is negative, the subject will remain in the study and continue to receive the study vaccines.
Rationale: This clarification has been added to provide clear guidance on the course of action in the event of a positive urine pregnancy test.	
Section 6.2.2 "Screening Laboratory Evaluations"	HbA1C has been added to the list of screening evaluations.
Rationale: To identify and exclude people with undiagnosed diabetes from the study. People meeting this criteria will be referred for follow-up care.	
Section 6.2.3 "Safety laboratory evaluations"	Section 6.2.3 has been removed and replaced with new section 6.2.4. "Clinical laboratory sub-study".
Rationale: Baseline and Day 7 safety laboratories for the full study cohort have been replaced with a more intensive laboratory assessment in a subset of the full study cohort as part of a clinical laboratory sub-study (at select sites). Laboratory parameters in the sub-study are being assessed at V1 (Study Day 0) and 1 week after each vaccination (Study Days 7, 35, 175).	

6.2.5 "Biological samples, handling, analysis and storage"	Changes made to reflect new sample requirements for clinical laboratory assessments (clinical laboratory sub-study, select sites) one week after each vaccination.
Rationale: Changes made to reflect sample requirements for the main study and the clinical laboratory sub-study.	
Section 6.3.1 "Screening"	Addition of Urinalysis to the list of tests to be done at screening.
Rationale: Addition was made for consistency with the Appendix 1 Schedule of Events and Section 6.2.2 Screening Laboratory Evaluations.	
Section 6.3.2 "Vaccination Visits"	Clarification provided that inactivated vaccines should not be received 2 weeks prior to 2 weeks after any study vaccination or attenuated vaccines within 4 weeks of any vaccination.
Rationale: Sentence restructured to improve clarity.	
Section 6.3.2 "Vaccination Visit"	Clarification is provided that urine pregnancy must not only be reviewed, but also be confirmed to be negative prior to vaccination.
Rationale: To provide clarity on the rationale for inclusion of this pre-vaccination test in women of childbearing potential.	
Section: 6.3.3 "Safety Follow-up"	In the main study, the safety follow up will now consist of a telephone follow up call 7-days after each vaccination in the full study cohort. Laboratory assessments 1 week after each vaccination will be carried out at select sites (clinical laboratory sub-study).
Rationale: Modification made to reflect implementation of clinical laboratory sub-study (select sites) and removal of the 7-day laboratory evaluation in the full study cohort. A 7-day follow-up telephone call is now done after each vaccination in the main study.	
New Section 6.3.6 "Sub-study additional visits" added and new Section 6.3.7 "End of Study visit"	Additional study visits for clinical laboratory sub-study at select sites are now defined. End of study visit is now Section 6.3.7.

Rationale: To clarify the additional visit requirements for the clinical laboratory sub-study.	
Section 6.3.6 End of Study Visit	Clarification provided that lack of seroprotection corresponds to an anti-HBs level <10 mIU/mL and not <10 IU/mL.
Rationale: Correction of typographical error.	
Section 7.2.2 "Vital Signs and Vaccine Reactions"	Clarification provided that 1) vital signs are recorded for 30 minutes following each vaccination, 2) recording of solicited reactions and temperature monitoring are required daily to day 6 post vaccination and 3) unsolicited adverse events are recorded for 27 days post vaccination.
Rationale: Clarification is provided as to the nature/intensity and duration of safety monitoring required during the conduct of the study.	
Section 7.7 "Unblinding"	The word 'serious' was added to define Suspected, Unexpected, Serious, Adverse Reaction (SUSAR)
Rationale: Correct definition of SUSAR provided.	
Appendix 1 Schedule of Events	Addition of HbA1C to the list of evaluations at screening.
Rationale: HbA1C was included as part of the screening evaluations in order to identify and exclude people meeting the study exclusion criteria from participating in the study.	

1 BACKGROUND AND RATIONALE

1.1 Epidemiology

Hepatitis B virus (HBV) is a human double-stranded enveloped DNA virus that causes an acute infection which, in some cases, may develop into a chronic disease.

Approximately 260 million people are chronically infected by the HBV, worldwide[1]. In 2013, it is estimated that 686,000 people of all ages died from complications of hepatitis B, such as liver cirrhosis and liver cancer[2]. The progressive implementation of universal immunization programs in infants, children and adolescents in a total of 184 countries[1] has resulted in vaccine coverage of 82% of children, and a drop in the incidence of hepatitis B in these countries. However, adults who were not immunized as children against hepatitis B remain at risk of becoming infected with hepatitis B. According to the European Centre for Disease Prevention and Control, 25–34-year-olds are the most affected age group for both acute and chronic hepatitis B infections, accounting for 33.8% of the 22,442 cases reported in 2014 by the 30 EU/EEA Member States[3].

1.2 Immunogenicity of licensed vaccines

Monovalent HBV vaccines, such as Engerix-B®, licensed in Canada, European Union (E.U), and the United States (U.S.) are second-generation vaccines using recombinant DNA technology to express the HBV DNA sequence coding for the small hepatitis B surface antigen (HBsAg) in yeasts. For Engerix-B®, the 1 mL dose containing 20 µg of HBsAg is the formulation approved for the immunization of healthy adults. In adults, the most commonly recommended immunization schedule consists of three injections of vaccine: two injections 4 weeks apart, followed by a third injection 24 weeks after the initial injection.

A serum concentration of hepatitis B surface antigen antibody (anti-HBs) ≥10 mIU/mL after vaccination is considered protective[4], and is associated with long term immunity to hepatitis B[5]. Therefore, the seroprotection rate (SPR), i.e., the percentage of subjects achieving a serum concentration of hepatitis B surface antigen antibody (anti-HBs) ≥10 mIU/mL after vaccination, is widely used as a surrogate endpoint for evaluating anti HBV vaccines.

While the SPRs elicited by currently licensed hepatitis B vaccines in children and adolescent are high (≥98%)[6], up to 10% of all adults fail to achieve anti-HBs levels ≥10 mIU/mL after a three-dose schedule[6], and are considered non-responders to hepatitis B vaccination. The proportion of adult non-responders is even higher in individuals age 30 years and above, where there is a well-documented age-dependent decline in response rate to currently licensed HBV vaccines[7,8]. In recent phase 3 trials where Engerix-B® was the comparator, SPRs 4 weeks after completion of the three-dose regimen were 74%, 72% and 68%, in adults 40-49, 50-59 and 60-69 years old, respectively[8-10]. In addition to age and genetic factors, other factors are known are known to be associated with reduced immunogenicity of HBV, including obesity[11], and, as recently reviewed by Yang Tian et al in 2016, male gender, smoking, diabetes, and concomitant disease[12].

Moreover, compliance with the primary three-dose schedule is low, with up to 40% of vaccinees missing the third injection, resulting in inadequate clinical protection against HBV infection[13].

The current recommendation in Canada is that non-responders are given another full three-dose schedule, with a rate of success of 50% to 70%[17]. In the U.S., recent Center for Disease Control guidelines for health care professionals recommend either to give another full three-dose schedule, or to utilize an incremental approach consisting of: 1) giving one additional vaccine dose followed by anti-HBs testing 1–

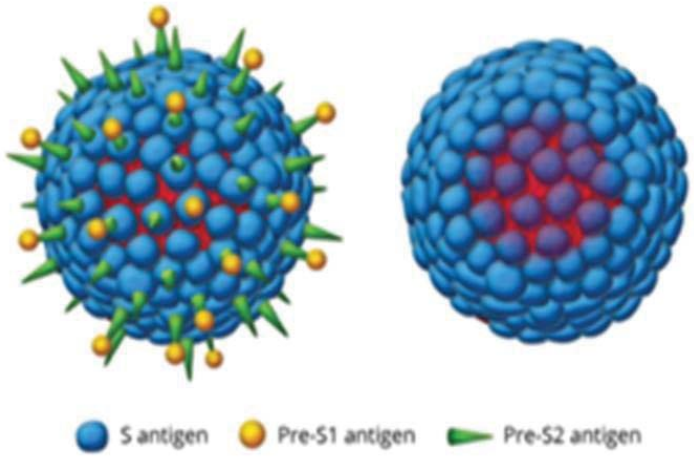
2 months later and 2) in the individuals whose anti-HBs levels remains <10 mIU/mL giving two additional vaccine doses, followed by repeat anti-HBs testing 1–2 months later. Similar re-vaccination strategies are also used in Europe. Re-vaccination in adult non-responders has variable response, is costly and delays the time to protection against hepatitis B infection. A more potent hepatitis B vaccine that is safe, more immunogenic, protects faster and with fewer injections and eliminates the need for re-vaccination therefore has important public health implications.

1.3 Sci-B-Vac™

1.3.1 Description

Sci-B-Vac™ is a third-generation hepatitis B vaccine, that is produced in mammalian Chinese hamster ovary (CHO) cells genetically modified to produce the three HBV envelope proteins (the small S Hepatitis B surface antigen, and the Pre-S2 and Pre-S1 proteins), unlike the second-generation hepatitis B vaccines that contain only the small S Hepatitis B virus surface antigen (see Figure 2). Sci-B-Vac™ is currently approved and marketed in Israel, Chile, Central Africa, Ivory Coast, Ethiopia, Georgia, Gabon, Guinea Equatorial, Hong Kong, Moldova, Niger, Nigeria, Philippines and Senegal, in 3 dosages: 2.5 µg and 5 µg HBsAg/0.5 mL for use in neonates, infants and children up to 10 years of age, and 10 µg HBsAg/1 mL for individuals age 10 years and older.

Figure 2: Sci-B-Vac™ (left) compared to a 2nd generation HBV vaccine (right)



1.3.2 Overview of clinical pharmacology

As described above in Section 1.3.1, Sci-B-Vac™ not only contains the S protein present in currently licensed second-generation HBV vaccines, but also contains pre-S1 and pre-S2 proteins that mimic the hepatitis B virion. The putative biological function and incremental significance of the immune response to each of the envelope proteins (i.e., S, pre-S2 and pre-S1) has been described previously.[14] Initial studies have shown that the pre-S antigens, and particularly pre-S1, express highly immunogenic T and B cell epitopes, a feature that could influence the immunogenicity and protection following administration of Sci-B-Vac™ [15,16]. Synthetic pre-S antigens have been found to protect chimpanzees against HBV challenge[18]. In addition, the pre-S2 protein has the following properties: 1) it binds polymerized human serum albumin in vitro; and 2) the pre-S2 has a domain that can also act as a B cell epitope. These

properties may contribute to an enhanced immunogenicity of pre-S2 [19,20]. Pre-S2 may also help in the attachment of HBV to hepatocytes, which may be prevented through an adequate anti-pre-S2 response[21]. Moreover, the pre-S1 domain of the envelope protein plays a critical role in binding the virus to its hepatocyte receptor, which may be disrupted in the presence of anti-pre-S1 antibody[22]. Finally, antibody responses to pre-S1 and pre-S2 may also reduce the risk of HBV infection caused by virus mutants in which the main neutralizing "a" conformational epitope (aa 124-147), within the major hydrophilic region (MHR) of the S protein, may escape antibody neutralization[23].

Since its original development in 1989, Sci-B-Vac™ has undergone a number of changes in formulation, manufacturer and proprietary name. The original formulation used aluminum phosphate ($AlPO_4$) as its adjuvant and contained thimerosal. The adjuvant was switched to aluminum hydroxide ($Al(OH)_3$) in 1994 and thimerosal was eliminated in 1998. Aluminum hydroxide remains the adjuvant in the current Sci-B-Vac™ formulation. Product distribution data globally estimates that over 500,000 infants, children and adults have been vaccinated with Sci-B-Vac™.

1.3.3 Potential risks and benefits

The potential risks and benefits are described in the Sci-B-Vac™ Investigator Brochure.

1.4 Rationale for conducting the study

A series of clinical trials with Sci-B-Vac™ conducted in adults, children and neonates over the past 2 decades have found that the currently approved three-dose regimen (administered on Days 0, at 4 weeks and 24 weeks) elicits very high seroprotection rates that are comparable to those elicited by second-generation vaccines, such as Engerix-B® or Recombivax-HB®.

More importantly, however, antibody responses following Sci-B-Vac™ administration in both the previous and current formulations of Sci-B-Vac™ are generally higher and faster following the first and second injections and may not decrease with age. These attributes suggest that Sci-B-Vac™ may help to raise seroprotection rates in adults with poorer or delayed response to second-generation vaccines, including older adults, patients with diabetes mellitus, obese individuals, and smokers. The safety profile of Sci-B-Vac™ is similar to second-generation vaccines, aside from being associated with a higher frequency of pain at the injection site in the earlier formulations.

The sponsor, VBI Vaccines Inc., is proposing two phase III clinical trials to generate additional safety and efficacy data for the current adult Sci-B-Vac™ formulation [1 mL, 10 µg HBsAg, aluminum hydroxide adjuvant, without thimerosal] in the adult population prior to seeking licensure in Canada, the U.S. and the E.U.

The current study is being undertaken to verify that the manufacturing equivalence of Sci-B-Vac™ is consistent, and 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.

2 OBJECTIVES

2.1 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 injection, 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];

2.2 Secondary objectives

Immunogenicity

To demonstrate that the SPR 4 weeks after completion of the three-dose regiment 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 in the 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®

2.3 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®.

Each of the above exploratory objectives will be assessed for each Sci-B-Vac™ lot separately, as well as for the difference between each Sci-B-Vac™ lot. In addition, they will also be assessed for all 3 lots of Sci-B-Vac™ pooled together, for the Engerix-B® group and for the difference between all 3 pooled lots of Sci-B-Vac™ and Engerix-B®.

3 STUDY DESIGN AND ENDPOINTS

3.1 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 the Hepatitis B virus (HBV), according to a three-dose immunization schedule, and followed for 24 weeks after the third vaccination.

Randomization will be stratified by study center.

The 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.

Upon confirmation of enrollment, each subject will be asked to come for a total of 5 visits (noted V1, V2, V3, V4, and end of study, V5). Subjects will be followed a minimum of 48 weeks after the first vaccination on Study Day 0, with at least 24 weeks of follow-up safety assessments after the third vaccination.

Immunization will consist of three single dose treatments with one of three different Sci-B-Vac™ lots or Engerix-B®. Each subject will receive one injection of 1 mL of Sci-B-Vac™ or Engerix-B® injected intramuscularly (IM) in the deltoid muscle at 0, 4 weeks (Study Day 28), and 24 weeks (Study Day 168). Subjects will remain in the clinic at least 30 minutes after each vaccination for rare adverse reactions.

There will be a safety follow-up by telephone 7 days after each vaccination to inquire about local and systemic reactions. Based on these follow up assessments, subjects may be asked to come for a supplemental visit for clinical assessment if warranted. In addition, the study center will also contact the subject 4 weeks after the second vaccination to assess the subject's status.

Immunogenicity (measurement of anti-HBs levels and characteristics) will be assessed on Study Days 0, 168, 196 and 336. A validated quantitative hepatitis B surface antibody (anti-HBs) test will be used to measure the level of anti-HBs (see below primary endpoint).

Safety evaluations will include standardized methods for local and systemic vaccine reactions, repeated vital signs and physical examinations, 48 week follow-up for SAEs, medically significant event or new onset of chronic illness (at least 24 weeks after the third dose of vaccine), and changes in concomitant medication.

At select sites, study subjects will also participate in a clinical laboratory sub-study. All subjects enrolled at these sites will be asked to come for three additional visits (denoted A1, A2, A3 in Appendix 1 Schedule of Events) 1 week after each vaccination, and to provide 4 additional blood samples, at V1 (Day 0) and at A1, A2 and A3, on Study Days 7, 35 and 175, respectively. The clinical laboratory sub-study will include at least 10% of the total number of subjects enrolled to the trial and will assess hematology and biochemistry laboratory parameters over the full three-dose vaccination schedule.

The total study duration for each subject (assuming a screening period of 28 days) is 364 days. The schedule of assessments and timelines are detailed in section 6.3 and in Appendix 1: Schedule of Events .

3.2 Immunogenicity endpoints

- Geometric Mean Concentration (GMC) of anti-HBs in serum after 2 vaccinations, just prior to receiving the third vaccination, and 4 weeks and 24 weeks after the third vaccination with Sci-B-Vac™ or Engerix-B®, on Study Days 168, 196, and 336, respectively. The GMC at Study Day 196 is the basis for assessing lot-to-lot consistency of the three consecutive lots of Sci-B-Vac™.

- Seroprotection rate after 2 vaccinations, just prior to receiving the third vaccination, and 4 weeks and 24 weeks after the third vaccination with Sci-B-Vac™ or Engerix-B®, on Study Days 168, 196, and 336, respectively. Seroprotection is defined as anti-HBs levels ≥ 10mIU/mL in serum. Seroprotection rate is the percentage (%) of subjects achieving seroprotection.
- Proportion of subjects achieving anti-HBs levels ≥ 100mIU/mL in serum after 2 vaccinations, just prior to receiving the third vaccination, and 4 weeks and 24 weeks after the third vaccination with Sci-B-Vac™or Engerix-B® on Study Days 168, 196, and 336, respectively.
- 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.
- 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®.

3.3 Safety endpoints

Standard clinical parameters for evaluating the safety of a biologic or vaccine product will be used, including the following: standardized methods for local and systemic vaccine reactions classified by severity within predefined categories, repeated vital signs and physical examinations, 48-week follow-up for SAE (at least 24 weeks after the third vaccination), and changes in concomitant medication. At select sites, subjects will be asked to come for 3 additional visits (denoted A1, A2, A3) to assess clinical laboratory parameters (hematology, biochemistry) one week after each vaccination (Study Days 7, 35 and 175), as part of a clinical laboratory sub-study.

- Number (%) of subjects who reported solicited AEs (on the day of vaccination and during the next 6 days), number (%) of unsolicited AEs (on the day of vaccination and during the next 27 days), and number (%) of SAEs, medically significant event (condition prompting emergency room visit, physician visit not related to a common disease/not a routine visit or an SAE not related to a common disease) or new onset of chronic illness (through Study Day 336). Adverse events will be classified by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, severity, seriousness, investigator and Sponsor causality assessment, and time since vaccination.
- Number (%) of subjects with abnormal vital signs; physical examination findings compared to baseline.
- Number (%) of subjects with abnormal clinical laboratory parameters from baseline assessments on Study Days 7, 35 and 175, one week after each vaccination with either Sci-B-Vac™ or Engerix-B® (Clinical laboratory sub-study, select sites)

4 STUDY ENROLLMENT AND WITHDRAWAL

4.1 Subjects population

The study will enroll approximately 3,200 subjects, 18-45 years old, in at least 30 study centers in the E.U., Canada and the U.S. Both men and women of all races and ethnic groups are eligible for this trial.

Adherence to inclusion and exclusion criteria is essential to ensure safety to the subjects and precise comparison of control and treatment groups. Deviations from inclusion and exclusion criteria are not allowed because they could jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Inclusion and exclusion criteria are defined below.

4.1.1 Inclusion criteria

Subjects must meet all the following criteria to be eligible:

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 (12 months with no menses without an alternative medical cause) 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.

4.1.2 Exclusion criteria

Subjects meeting any of the following 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.
7. Has received blood products or immunoglobulin within 90 days prior to study entry or likely to require blood products during the study period.
8. Subject in another clinical trial with an investigational drug or a biologic within 30 days of enrollment.
9. Has received granulocyte-macrophage stimulating factor (G/GM-CSF) or erythropoietin (EPO) within 30 days of enrollment or likely to require GM-CSF erythropoietin during the study period.
10. Any history of cancer requiring chemotherapy or radiation within 5 years of randomization or current disease. Subject with an history of low risk basal cell carcinoma will be accepted (low risk being defined by the following: 1) location on the trunk of the body, arms, legs, cheeks, forehead, temples, scalp, neck or chin and 2) less than 2 cm, and 3) nodular or superficial, and 4) primary cancer that has not come back after treatment and 5) edge of the cancerous area is clear and smooth and 6) not located in or around nerves).
11. Any skin abnormality or tattoo that would limit post-vaccination injection site assessment.
12. History of allergic reactions or anaphylactic reaction to any vaccine component.
13. Unwilling, or unable in the opinion of the investigator, to comply with study requirements, including the use of an adequate birth control method.
14. Immediate family members of study center staff (parents, sibling, children).
15. Current or past hepatitis B infection or prior vaccination as evidenced by HBV infection markers (anti-HBc, anti-HBs , HBsAg) at screening.
16. Known hepatitis C infection or positive Hepatitis C serology at screening, unless treated and cured (defined as documented sustained virologic response (SVR) or negative viral load ≥ 12 weeks after cessation of antiviral therapy).
17. Known human immunodeficiency virus (HIV) infection or positive HIV serology at screening.
18. Renal impairment with glomerular filtration rate (GFR) of <60 mL/min/1.73m^2
19. Body mass index (BMI) ≥ 35.
20. Uncontrolled hypertension (defined as an average SBP ≥ 150 mmHg or an average DBP ≥ 95 mmHg based on the last three measurements in people diagnosed and treated for hypertension, and in people without a diagnosis of hypertension).
21. Diagnosis of Type 1 or Type 2 diabetes or HbA1C ≥ 6.5% at screening.

22. Any laboratory test abnormality that would be considered of Grade 1 severity or above as per FDA guidelines for grading clinical laboratory abnormalities (see Appendix 3 in Protocol) **AND** is considered as clinically significant by the investigator. Grade 3 severity or above is exclusionary, regardless of clinical assessment.

4.2 Enrollment procedures

Eligible subjects must be informed of the study, including the schedule of visits, the required evaluations, the risks, the alternative options, and all the regulatory aspects of consent. Written consent must be obtained prior to enrollment. Consenting subjects will be informed that the study site staff will provide them with their serology results at the end of the study, once the database has been locked.

Assessments to confirm eligibility should be completed within 4 weeks of the first vaccination visit on Study Day 0. To complete enrollment, an investigator will confirm eligibility criteria, and an authorized member of the study team will access the enrollment page in the interactive web response system (IWRS).

The authorized staff will be prompted to complete the enrolment page in the IWRS, including the subject's year of birth and other demographic data, and to confirm individually the presence of all inclusion criteria and the absence of all exclusion criteria. Upon confirmation that all inclusion criteria and no exclusion criteria are met, the subject will be randomized to one of the four study arms. A confirmation of the randomization (blinded) will be sent by E-mail to the site. The confirmation of enrolment should be retained in the study files. The dedicated unblinded site staff and/or pharmacy (if applicable) will receive a confirmation notification, which must be filed in a locked area/computer folder not accessed by blinded study center staff.

4.3 Subject withdrawal

Subjects who are withdrawn because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as result of a SAE/AE until resolution or stabilization of the event and will evaluate, record and report AEs and SAEs as instructed in Section 7 (ASSESSMENT OF SAFETY).

Withdrawals will not be replaced.

4.3.1 Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the end of study visit (V5)/was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Research center staff will make diligent attempts to contact those subjects who do not return for scheduled visits or follow-up. Attempts will be documented in source documents. A registered letter will be sent after four unsuccessful attempts to contact a subject by telephone. If unsuccessful, the subject will be considered lost to follow-up and withdrawn from the study. In order to mitigate the risk of subject lost to follow-up research center staff will obtain any relevant contact details, including, when allowed by applicable privacy and patients' rights laws and institutional policies alternate contact information for relatives, or relevant third parties (as determined by the subject) upon enrollment of the subject in the study. Study center staff will enquire about changes in contact information at each visit. Information will

be collected and stored in compliance with all applicable privacy and patients' rights laws and institutional policies.

Information relevant to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject, the investigator or the medical monitor, as well as which of the following possible reasons was responsible for withdrawal:

- SAE
- Non-serious AE
- Major protocol violation warranting withdrawal of the subject from the study, after consultation with the medical monitor (specify)
- Consent withdrawal, not due to an AE* (specify)
- Moved from the study area
- Lost to follow-up
- Request of regulatory agency, or Sponsor or Principal Investigator
- Subject is non-compliant with study procedures/study protocol
- Investigator decides that withdrawal from the study is in the best interest of the subject
- Any clinically significant change in subject's medical condition.
- Pregnancy
- Other (specify)

*In case a subject is withdrawn from the study because he/she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the eCRF.

4.3.2 Subject withdrawal from investigational product

A 'withdrawal' from the investigational product refers to any subject who does not receive the complete immunization schedule, i.e., when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the investigational product may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relevant to premature discontinuation of the investigational product will be documented on the Study Exit screen of the eCRF. The investigator will document whether the decision to discontinue further injection/treatment was made by the subject or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE
- Non-serious AE
- Pregnancy
- Other (e.g. subject found to have received a concomitant medication not permitted on study that required withdrawal from the investigational product, based on consultation with the medical monitor).

4.4 Termination of study or suspension of study

This study may be temporarily suspended or prematurely terminated by the sponsor, a regulatory agency, the data monitoring committee or an ethical body. Written notification documenting the reason for study suspension or termination will be provided by the suspending or terminating party to the investigator, the study sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the

investigator will promptly inform the relevant ethical body (see Section 13.1) and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, or data quality are addressed and satisfy the study sponsor, relevant ethical body and regulatory agencies.

Otherwise, the execution of the study will close after the last complete assessment of all the subjects. Laboratory measures, subsequent planned laboratory measures, data management and analysis will continue until final statistical report of the trial results.

This trial will be conducted in compliance with the protocol, good clinical practice (GCP) and the applicable regulatory requirements

5 STUDY AGENTS

Details concerning the ordering, shipping, receiving, storage and handling of study agents are detailed in the pharmacy manual.

5.1 Sci-B-Vac™

5.1.1 Acquisition

Sci-B-Vac™ will be supplied by the study sponsor.

5.1.2 Formulation and Labelling

Sci-B-Vac™ will be supplied as 1.0 mL single-dose vial containing 10 µg of hepatitis B surface antigen adsorbed onto 0.5 mg of aluminum as aluminum hydroxide ($Al(OH)_3$), sodium chloride, potassium chloride, disodium hydrogen phosphate dodecahydrate, potassium dihydrogen phosphate anhydrous and water for injection.

Three independent consecutive lots of Sci-B-Vac ™ will be used in the trial, each containing 10 µg of hepatitis B surface antigen with aluminum hydroxide ($Al(OH)_3$) as an adjuvant, delivered as a 1.0 mL intramuscular injection:

- Group A: Sci-B-Vac™ “Lot A”
- Group B: Sci-B-Vac™ “Lot B”
- Group C: Sci-B-Vac™ “Lot C”

All vials and secondary packaging will be labeled as required by applicable regulations (including the use of the appropriate official language(s)).

5.1.3 Product Storage

Sci-B-Vac™ should be stored at 2-8°C (36°and 46°F).

5.2 Comparator Engerix-B®

5.2.1 Acquisition

Engerix-B® will be purchased from commercial source(s) and supplied by study sponsor.

5.2.2 Formulation and Labelling

For the study, Engerix-B® will be provided as 1 mL vials. Engerix-B® will be delivered as an intramuscular injection.
Each 1-mL adult dose contains 20 µg of HBsAg adsorbed on 0.5 mg aluminum as aluminum hydroxide.
Vials and secondary packaging will be labeled as required by applicable regulations (including the use of the appropriate official language(s)).

5.2.3 Product Storage

ENGERIX®-B (hepatitis B vaccine recombinant) should be stored at 2 to 8°C (36° and 46°F).

5.3 Dosage, preparation administration of study vaccines

On the day study subjects are dosed, vaccine vials will be removed from the refrigerator. The treatment each subject will receive will be allocated by an IWRS tool. The unblinded study center staff/pharmacy staff will select the appropriate vial. The vial will be transported to the administration site by an unblinded study center staff as outlined in the pharmacy manual. Vaccine vials not utilized on a vaccination administration day (i.e., Study Day 0, 28, or 168) will be destroyed and documented as per study center policy following verification of product accountability (see Section 5.5).

Study vaccine will be administered by an unblinded qualified health personnel, whose sole role is to prepare for, and administer the allocated study vaccine, and to perform related activities that require vial handling. Preparation of the study vaccine must be done by the unblinded study center staff/pharmacy staff behind a screen or in a separate room from where blinded research staff and study participants will be located. The unblinded study center staff will thoroughly mix all study vaccines by swirling the vial for 30 seconds immediately before administration. The study vaccines should be visually inspected for discoloration prior to administration. The study vaccine should not be used if the vaccine appears discolored. After visual inspection a syringe will be used to withdraw the vaccine from the vial and then it will be covered and immediately administered to the subject. The unblinded health personnel will not communicate what vaccine was administered to the subject or study centre staff performing the outcome measurements. As such, subjects and all study personnel will not be aware of treatment assignment.

The first injection will be given in the deltoid of the non-dominant arm using the IM route by the unblinded health personnel. Subsequent injections will be administered IM in the deltoid but will be alternated between the non-dominant and dominant arms. The injection site will be recorded at each vaccination. The study vaccine should be administered immediately after withdrawing the 1-mL dose of vaccine from the single-dose vial. The study subject will not be told whether the study product is Sci-B-Vac™ or Engerix-B®.

5.4 Accountability procedures for the study vaccines

The site investigator is responsible for ensuring that all study vaccines received at the center are inventoried and accounted for throughout the study. Site staff must not combine contents of the study vaccine containers.

Study vaccine must be handled in strict accordance with the protocol and the container label and will be stored in a limited access area under appropriate environmental conditions as outlined in the pharmacy manual.

Study vaccine will be administered at the study center by qualified health personnel. Study vaccines will be supplied only to subjects participating in the study. Study vaccines may not be relabeled or reassigned for use by other subjects. The investigator agrees to ensure appropriate storage requirements and product accountability and to administer the study vaccine only at the centers agreed upon with the study sponsor.

5.5 Destruction of unused products

As outlined in the pharmacy manual, all empty vials will be destroyed and documented as per study center policy, following verification of product accountability by the unblinded clinical research associate (CRA). At the end of the study, all unused products will also be destroyed and documented as per study center policy, following verification and product accountability by the unblinded CRA.

If a vial is compromised, such as unreadable label or presence of particles in the study product, the study sponsor should be notified immediately. The vial should be photographed and stored separately in a labelled container. Following verification and product accountability by the unblinded CRA, all compromised vials will be destroyed and documented as per study center policy.

5.6 Rescue medications, treatments, and procedures

5.6.1 Safety Follow-up and management of reactions to vaccines

The following safety observation procedures will be performed immediately following vaccination with the study vaccine and during the 4 weeks following vaccine visits for all subjects:

Subjects will remain in the clinic for at least 30 minutes after vaccination. The observation period will include an assessment of immediate solicited local and systemic reactions. Any unusual signs or symptoms reported during the initial 30 minutes of observation will prompt continued close monitoring. Based on their condition, subjects may be asked to remain in the clinic for more than 30 minutes after the vaccination (reason will be recorded in source data). All data (including assessment of solicited local and systemic reactions) will be recorded in the source document during and after the post-observation period.

During the vaccination visits, subjects will be given 28-day diary cards. A measurement device template (in mm) for measuring solicited local reactions (erythema [redness] and swelling), and an oral thermometer for recording daily temperature (in ºC or in ºF) will be provided at the first vaccination at visit V1 (Study Day 0).

There will be a safety follow-up by telephone 7 days after each vaccination to inquire about local and systemic reactions. Based on these follow up assessments, subjects may be asked to come for supplemental visits for clinical assessment if warranted. In addition, the study center will contact the subject on Day 56 (+/- 3 days), 4 weeks after the second vaccination to assess subject's status.

Subjects will be advised to record their temperature daily in the diary, on the day of vaccination and for the next six days.

Refer to Sections 6.1.9 and 7 for further details on the recording, assessment, and reporting of adverse events and/or local and systemic reactions.

5.6.2 Management of non-responders

After the database has been locked individual serology results will be communicated to the study sites and subjects will be informed of their results by the study site staff. Study subjects that are found to not be seroprotected after completing the three-dose regimen (anti-HBs levels < 10mIU/mL in serum) will be offered re-immunization with Engerix-B® according to local guidelines. Engerix-B® will be supplied by the study sponsor.

6 STUDY PROCEDURES

6.1 Detailed description

6.1.1 Informed consent

The signed informed consent must be obtained before any study-related procedures.

6.1.2 Check inclusion and exclusion criteria

Verification of eligibility must be completed by the investigator or qualified designee prior to randomization. Prior to vaccine administration on Study Days 0, 28, and 168, eligibility for vaccine administration and continued participation in the study must be verified by the investigator or qualified designee.

6.1.3 Collect demographic data

Record demographic data such as age, gender at birth, height, weight, race, ethnicity, smoking history, tobacco use and average daily alcohol consumption in the subject's eCRF. Height (inches or cm) and weight (pounds or kg) will be measured at screening for automatic calculation of body mass index.

6.1.4 Medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the first study injection in the eCRF.

6.1.5 Physical examination

Full physicals will be done at the screening visit or at Study Day 0 (Visit 1) prior to injection; history-directed physical examination can be completed at subsequent visits. If the investigator determines that the subject's health on the day of injection temporarily precludes injection, the visit will be rescheduled. Collected information will be recorded in the eCRF.

6.1.6 Vital signs

Oral temperature, blood pressure (systolic/diastolic), heart rate, and respiratory rate will be assessed at baseline (Study Day 0) and at each vaccination visit and recorded in the eCRF. Any abnormal vital sign after injection should be reassessed.

The oral body temperature of all subjects will be measured prior to any study product administration. The subject should be instructed to refrain from eating or drinking 30 minutes prior to obtaining the temperature. If the subject has a fever (defined as temperature ≥38.0°C/100.4°F oral) on the day of injection, the vaccination visit will be rescheduled within the allowed treatment interval.

6.1.7 Treatment allocation

Treatment allocation will be done through IWRS. Access to the IWRS will be through individual login and password. To enroll a new subject, the authorized staff at the site will be prompted to complete a randomization page including the subject's age, and other demographic information and to confirm individually the presence of all inclusion criteria, and the absence of all exclusion criteria. Upon confirmation that all inclusion criteria and no exclusion criteria are met the subject will be randomized. Blinded confirmation of the randomization will be sent by E-mail to the site and should be retained in the study files. The site pharmacy and/or unblinded study center staff will receive a notification of the randomization, which must be filed in a locked area/computer folder not accessed by blinded study center staff.

6.1.8 Study product administration

After completing all prerequisite procedures, one dose of study vaccine will be administered IM in the deltoid of the non-dominant arm. Subsequent injections will be administered IM in the deltoid but will be alternated between dominant and non-dominant arms. This site of injection will be recorded at each vaccination visit. Reasons for subject refusal for site rotation will be documented in the eCRF. If the investigator or qualified designee determines that the subject's health on the day of administration temporarily precludes administration, the visit will be rescheduled within the allowed interval for the study visit.

Subjects will be observed for 30 minutes following the administration of their injection for rare adverse reactions. Appropriate medical treatment will be readily available in case of anaphylaxis.

6.1.9 Check and Record Concomitant Medication and Intercurrent Medical Conditions

Concomitant medication, including administration of other licensed vaccines, must be checked and recorded in the eCRF.

The use of the concomitant medications/products/vaccines listed below are not permitted on study and may result in withdrawal from the investigational product (see Section 4.3.2). The use of these concomitant medications will not require withdrawal of the participant from the study, but may determine a subject's evaluability in the per protocol set analysis. Subsequent study vaccinations in a subject that is found to have received any of the concomitant medications/products/vaccines listed below will be determined on an individual basis, after consultation with the medical monitor.

- Any investigational or non-registered product (drug or vaccine) other than the study product(s) used during the study period
- Any inactivated vaccine received 2 weeks prior to 2 weeks after a study vaccination.
- Any attenuated vaccine received 4 weeks prior to 4 weeks after a study vaccination.
- Immunosuppressant corticosteroids > 20mg/day prednisolone equivalent administered during the study (inhaled and topical steroids are allowed).
- Blood products, immunoglobulin, or GMCSF/EPO received during the study

Intercurrent medical conditions must be checked and recorded in the eCRF. Subjects may be eliminated from the per protocol analysis set for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or if they become diagnosed with an immunological disorder.

6.1.10 Recording of adverse events

- The subjects will be instructed to contact the investigator/study center staff immediately should they manifest any signs or symptoms they perceive as significant.
- During the vaccination visits (on Study Days 0, 28, and 168), the subject will be provided 28-day diary cards. On Study Day 0 they will also be provide with a measurement device template (in mm) for measuring the largest diameter of solicited local reactions (erythema [redness] and swelling), and an oral thermometer for recording daily temperature (in ºC or in ºF) on the day of vaccination and for the next 6 days.
- Subjects will be asked to record the maximum pain, tenderness and pruritus they experience at the injection site on a scale from 0 to 3 (0: no pain 1: Mild discomfort to touch 2: Discomfort with movement 3: Significant discomfort at rest) on the day of vaccination and for the next 6 days.
- The subject will record daily body temperature (oral) and any solicited local and systemic AEs (i.e., on the day of injection and during the next 6 days) and any unsolicited AEs (i.e., on the day of injection and during the next 27 days). The study center will also contact the subject by telephone 7 days after each vaccination to assess subject status and to remind the subject to complete the diary card and return it at the next study visit.
- The subject will be:
  - Trained on how to complete the diary
  - Requested to record their individual data in their diary cards, as described above.
  - Asked to provide a telephone contact, so the study center staff can contact them for the safety follow-up 7 days (+/- 2 days) after each vaccination, and 4 weeks (+/- 7 days) after the second vaccination.
  - Advised that they will be asked about the occurrence of any symptoms or events requiring medical attention (i.e., requiring a doctor or emergency room visit) and the use of concomitant medication up to Day 336.
  - Instructed to bring their diary cards to clinic visit on Study Days 28, 168, and 196 as follows: the diary card provided on Study Day 0 will be collected on day 28; the diary card provided on Study Day 28 will be collected on Study Day 168, and the diary card provided on Study Day 168 will be collected on Study Day 196. The staff will review the diary cards entries with the subject.
  - Advised on how to contact study center staff. Subjects will be advised to immediately contact the investigator (or his/her designee) in the event of a SAE or change in health.
  - Informed to notify their health care professional(s) (e.g., primary care physician) that they are participating in a clinical research study of an HBV vaccine.
  - Be informed of the appointments (date and time) for the next planned visits to the study center (Days 28, 168, 196, and 336). At select sites, subjects will also be required to come

for 3 additional visits one week after each vaccination (Study Days 7, 35 and 175) to provide a blood sample for the clinical laboratory sub-study.

- Any unreturned diary cards will be sought from the subject through telephone call(s) or any other convenient procedure.

Diary cards will be available in all official languages of participating countries. The investigator/study center staff will transcribe the collected information into the eCRF in English. AEs transcribed to English from the diary card will be verified for accuracy during the site monitoring visit.

- Diary cards are considered source documents.

6.2 Laboratory evaluations

6.2.1 Urine pregnancy test

In females of childbearing potential urine pregnancy tests must be confirmed negative at screening, and prior to study vaccine administration on Study Days 0, 28, and 168. A confirmatory serum pregnancy test will be required in the event of a positive urine pregnancy test. A positive serum pregnancy test will result in withdrawal of the subject from the study (per section 4.3.1). A negative serum pregnancy test will permit the subject to continue on the study and to continue to receive the study vaccines. In women whose urine pregnancy tests is positive, no study vaccine will be administered until the confirmatory serum pregnancy tests is found to be negative.

6.2.2 Screening laboratory evaluations

The following laboratory evaluations will be done at screening:

- All potential subjects will be tested for HIV infection, HCV infection and past or current HBV infection prior to enrollment. A positive test is exclusionary, except in the case of HCV, if the subject was treated and cured (defined as documented sustained virologic response (SVR) or negative viral load ≥ 12 weeks after cessation of antiviral therapy)
- Hematology
  - White blood cell count with differential
  - Red blood cell count
  - Hematocrit (HCT)
  - Mean cell hemoglobin (MCH)
  - Mean cell hemoglobin concentration (MCHC)
  - Mean corpuscular volume (MCV)
  - Hemoglobin
  - Platelet count
- Biochemistry:
  - Blood urea nitrogen (BUN)
  - Serum creatinine
    - GFR: will be automatically calculated upon input of serum creatinine value, age, gender and race in the eCRF using CKD-EPI Creatinine Equation (2009)[24]
    - GFR < 60 mL/min/1.73 m^2 is exclusionary
  - Alkaline phosphatase (AP), alanine transaminase (ALT), aspartate transaminase (AST), total and conjugated bilirubin, gamma-glutamyl transferase (GGT)

  - HbA1C will be tested at screening to identify people with undiagnosed diabetes. HbA1C ≥ 6.5% is exclusionary. People found to have HbA1C ≥ 6.5% will be referred for follow up care.
- Urinalysis:
  - A urine sample will be tested for: pH, gravity, glucose, ketones, nitrites, bilirubin urobilirubin, blood, protein, red blood cell count, white cell count.

Any anomaly that would be considered of Grade 1 severity (or more) according to Appendix 3 will be interpreted within the subject's specific context (e.g. subject's medical history, physical examination, other laboratory tests) by the investigator to determine whether the subject still meets the inclusion criterion # 3. Grade 3 severity or above is exclusionary, regardless of clinical assessment. One repeat testing assessment will be permitted.

6.2.3 Immunogenicity

Immunogenicity (measurement of hepatitis B surface antibody (anti-HBs) levels and characteristics) will be assessed on Study Day 0 (V1), on Day 168 (V3) just before the third vaccination, and 4 weeks and 24 weeks after the third vaccination on Days 196 (V4) and on Day 336 (V5 end of study visit), respectively.

A validated quantitative hepatitis B surface antibody test will be utilized to measure anti-HBs levels in serum.

6.2.4 Clinical laboratory sub-study

At select study sites, clinical laboratory parameters (hematology, biochemistry) will be assessed one week after each vaccination with either Sci-B-Vac or Engerix-B® and compared to baseline (pre-vaccination) values, as part of a clinical laboratory sub-study. All subjects enrolled at these select sites will be required to come for three additional visits and to provide four additional blood samples, beyond those required for the main study. The clinical laboratory sub-study will include at least 10% of all subjects enrolled to the entire trial.

Blood samples for the clinical laboratory sub-study will be collected at baseline (Study Day 0, Visit 1) prior to receiving any study vaccine, and at each of the three additional visits (additional visits A1, A2 and A3 in Appendix 1 Schedule of Events), to be scheduled 1 week after each vaccination with Sci-B-Vac™or Engerix-B® on Study Day 7 (-3/+7 days), Study Day 35 (-3/+7 days) and Study Day 175 (-3/+7 days), respectively. The following clinical laboratory parameters will be evaluated:

- Hematology
  - White blood cell count with differential
  - Red blood cell count
  - Hematocrit (HCT)
  - Mean cell hemoglobin (MCH)
  - Mean cell hemoglobin concentration (MCHC)
  - Mean corpuscular volume (MCV)
  - Hemoglobin
  - Platelet count
- Biochemistry:
  - Blood urea nitrogen (BUN), serum creatinine.
  - Alkaline phosphatase (AP), alanine transaminase (ALT), aspartate transaminase (AST), total and conjugated bilirubin, gamma-glutamyl-transferase (GGT)

Safety laboratory evaluations may be repeated if indicated (e.g. follow-up of a clinically significant laboratory abnormality (from baseline assessment))

6.2.5 Biological samples handling, storage and analysis

For the main study, the total amount of blood will not exceed 15 mL at any given visit. For select sites participating in the clinical laboratory sub-study, an additional 10 mL of blood will be required at V1 (Study Day 0) and at each of the additional study visits (A1, A2, A3) on Study Days 7, 35, and 175, respectively.

Samples and accompanying documentation will not be labeled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

Unused blood samples will be stored up to 60 months (5 years) after the study has been completed for re-testing purposes, after which the samples will be destroyed.

If consent is withdrawn after a blood sample has been taken, but before the samples are sent for testing, the study doctor will arrange to have the samples destroyed. If consent is withdrawn after the samples have been sent for testing, the Sponsor and the study doctor will ensure that the sample is destroyed. However, if the testing has been performed, the Sponsor is not obliged to destroy the results of this research. In this case, only the sample will be destroyed.

A central laboratory manual will be provided to the clinical sites detailing the handling, analysis, storage and shipping of blood samples for immunogenicity testing. Screening and safety laboratory blood samples will be collected, processed and analyzed according to local standard operating procedures. Each clinical site will be provided with the conversion factors to SI (International System of units) to facilitate the grading of blood chemistry and hematology abnormalities, according to the FDA guidelines.

6.3 Study schedule of events

A schedule of events is available in Appendix 1.

6.3.1 Screening

The screening will be conducted within 28 days (4 weeks) of Visit 1 (V1). After obtaining informed consent in accordance with ICH GCPs, inclusion/exclusion criteria will be assessed and the following data/samples will be obtained:

- Medical History/ Demographics
- Physical Examination (or at V1 prior to injection)
- Height and weight
- Concomitant medications
- Urine Pregnancy test (in females of childbearing potential)
- Blood sampling for safety laboratory tests and serology testing (HIV, Hepatitis C and B)
- Urinalysis

If the subject is eligible, the study staff will proceed to complete the enrollment procedures and to schedule the first vaccination visit. Study subjects will be requested not have any inactivated vaccines (e.g.

influenza) 2 weeks prior to 2 weeks after each study vaccination and not to have attenuated vaccines (e.g. MMR) 4 weeks prior to 4 weeks after each study vaccination. For tests conducted during screening to establish eligibility, one re-test will be permitted during the screening window (-28 Days to 0). If a re-test is performed, the second result of the test will be used to establish subject eligibility for study participation. The reason for the re-test (e.g., suspected hemolysis of a blood sample; inadequate urine specimen) will be recorded in the eCRF. Approval from the Sponsor or their delegate should be sought before performing the re-test.

6.3.2 Vaccination visits

Vaccination will be administered at Visit 1, 2 and 3 (Study Day 0, Study Day 28 (-3 days/+7 days), and Study Day 168 (+/- 7 days, respectively)).

On Day 0 (V1), subjects will have a blood sample collection prior to vaccine administration.

At subsequent vaccination visits (on Study Days 28 and 168), and prior to study vaccine administration, there will be a review of ongoing eligibility to receive the study vaccine and continue on the study. Diary cards will be collected and there will be a review of any local and systemic reactions. There will also be a blood sample collection prior to the third vaccine administration (Study Day 168).

Subject will remain in the clinic at least 30 minutes after each vaccination to be observed for rare adverse reactions.

The following will be done at each vaccination visit:

- Concomitant medications and any adverse reactions will be recorded
- A urine pregnancy test will be done in females of childbearing potential and reviewed prior to vaccination. Pregnancy test must be confirmed negative prior to study vaccine administration.
- Blood samples will be taken prior to vaccination on Study Days 0 and 168, for baseline anti-HBs levels and characteristics (Study Day 0) and measurement of anti-HBs measurement levels and characteristics just prior to the third vaccination (Study Day 168).
- Blood samples for assessment of clinical laboratory parameters will be taken on Study Day 0, prior to vaccination (select sites).
- Physical/History-directed physical examination will be done.
- Vital signs will be assessed before and after the injection of study vaccine. Any abnormal vital sign after injection should be reassessed.
- Eligibility for receiving treatment will be reviewed by the investigator.
- Study vaccine will be administered
- Subject will be observed for 30 minutes after the injection
- A new diary will be provided
- The next visit will be scheduled

- Subjects will be reminded that they should return the diary card at the next visit and that they should not receive any inactivated vaccine 2 weeks prior to 2 weeks following the first, second or third vaccination. Subjects will also be reminded not to have an attenuated vaccine between V1 (Study Day 0) and V2 (Study Day 28), 4 weeks following the second vaccination or within 4 weeks of the third vaccination.

6.3.3 Safety follow-up

The study center will contact the subject by telephone 7 days after each vaccination to assess subject's status and to remind the subject to complete the diary cards. A scripted set of questions will be asked over the telephone to determine health status and safety clinical markers.

In addition, the study center will contact the subject 4 weeks (+/- 3 days) after the second vaccination to assess subject's status. A scripted set of questions will be asked over the telephone to determine health status and safety clinical markers.

6.3.4 Supplemental visit(s)

Subjects may be asked to come for additional visit(s) for clinical assessment of an AE if warranted based on the telephone follow up safety assessment. The supplemental visit will be recorded in the eCRF.

6.3.5 Immunogenicity and safety visit post third vaccination

An immunogenicity visit (V4) will be scheduled 4 weeks after the third vaccination, on Day 196 (+/- 7 days):

- Physical/History-directed physical examination
- Blood samples for measurement of anti-HBs levels and characteristics will be taken.
- Diary will be reviewed.
- Adverse events and the use of concomitant medications will be recorded in the eCRF
- Visit 4 should be scheduled at least 3 weeks after the third vaccination (Visit 3)

6.3.6 Sub-study additional visits

At select sites, study subjects will also participate in a clinical laboratory sub-study. All subjects enrolled at these sites will be asked to come for three additional visits (denoted A1, A2, A3 in Appendix 1 Schedule of Events) beyond those required for the main study and to provide 4 additional blood samples, at V1 (Study Day 0) and at A1, A2 and A3, on Study Day 7 (-3/+7 days), Study Day 35 (-3/+7 days) and Study Day 175 (-3/+7 days), respectively. These blood samples will be used to investigate and compare clinical laboratory parameters (hematology, biochemistry) following vaccination with Sci-B-Vac™ and Engerix-B®.

6.3.7 End of study visit

The end of study visit (V5) will be performed on Day 336 +/-14 days or earlier in case of withdrawal.

- Physical/History-directed physical examination
- Blood samples for measurement of anti-HBs levels and characteristics will be taken.
- Serious Adverse Events, AE requiring medical attention and the use of concomitant medications will be recorded in the eCRF

- In case of withdrawal: reason for withdrawal will be documented in the ecRF
- Subject will be advised that the study center staff may need to contact them in case new information, such as an anti-HBs levels <10 mIU/mL, becomes available.

7 ASSESSMENT OF SAFETY

7.1 Specification of safety parameters

7.1.1 Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding);
- Symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product;
- Pre-existing symptoms or conditions which worsen during a study.

7.1.2 Serious Adverse Events

A Serious Adverse Event:

- Results in death;
- Is life threatening;

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

- Requires subject hospitalization or prolongation of existing hospitalization;

Note: In general, hospitalization signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Hospitalizations for routine procedures and investigations are not considered a SAE in this protocol.

- Results in persistent or significant disability/incapacity;

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/ birth defect.
- Is an important medical event

Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Should the investigator feel that an AE may jeopardize the subject or may require intervention to prevent more serious outcomes, then the AE should be treated as serious.

7.1.3 Pre-existing conditions

In this trial, a pre-existing condition (i.e. a disorder present before the AE reporting period started) should not be reported as an AE unless the condition worsens during the AE reporting period.

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen are not considered as AE.

7.1.4 Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as an AE. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE and the resulting appendectomy noted under comments.

7.1.5 Laboratory test abnormalities and other abnormal assessments

In subjects participating in the clinical laboratory sub-study, laboratory test value abnormalities and other abnormal assessment will be reported as AE, if they satisfy one or more of the following conditions for clinical significance:

- Accompanied by clinical symptoms;
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment);
- In absence of clinical symptoms or change in concomitant therapy if the investigator judges it to be clinically significant;
- Clinically significant abnormal laboratory findings and other abnormal assessment present at baseline and significantly worsening following the start of the study.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding is clinically significant.

7.1.6 Grading of AEs

7.1.6.1 Unsolicited Adverse Events

These AE will be graded according to the severity scale in Table 1.

Table 1: Unsolicited AEs severity scale

Grade 1 (Mild)	No interference with daily activity
Grade 2 (Moderate)	Some interference with daily activity but not requiring medical intervention

Grade 3 (Severe)	Prevents daily activity and requires medical intervention
Grade 4 (Potentially life threatening)	Requiring Emergency Room (ER) visit or hospitalization

7.1.6.2 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) 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) - see Appendix 2.

7.1.6.3 Laboratory tests abnormalities

Laboratory tests abnormalities will be graded according to the FDA guidelines for grading clinical laboratory abnormalities (Appendix 3).

7.1.7 Assessment of the outcomes

The investigator will assess the outcome of all AEs (including SAEs) recorded during the study as:

- Ongoing
- Recovered/resolved to pre-immunization health status
- Recovered/Resolved with sequelae
- Recovering/Improving
- Stabilized
- Unknown/Lost to Follow-up
- Fatal (SAE)

7.1.8 Causality

Relationship of all AE and SAE to the study interventions (causality) should be assessed by the investigator and the sponsor according to the criteria below:

- **Very likely/Certain:** A clinical event with a plausible time relationship to vaccine administration and which cannot be explained by concurrent disease or other drugs or chemicals.
- **Probable:** A clinical event with a reasonable time relationship to vaccine administration; and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- **Possible:** A clinical event with a reasonable time relationship to vaccine administration, but which could also be explained by concurrent disease or other drugs or chemicals.
- **Unlikely:** A clinical event whose time relationship to vaccine administration makes a causal connection improbable, but which could be plausibly explained by underlying disease or other drugs or chemicals.
- **Unrelated:** A clinical event with an incompatible time relationship and which could be explained by underlying disease or other drugs or chemicals.
- **Unclassifiable:** A clinical event with insufficient information to permit assessment and identification of the cause.

7.1.9 Unexpectedness

Adverse events and SAEs will also be assessed according to the following categories:

For Sci-B-Vac ™

- **Expected (anticipated):** the event is identified in nature, severity, and frequency in the investigator brochure or in the protocol.
- **Unexpected (unanticipated):** the event is not identified in nature, severity, or frequency in the investigator brochure or in the protocol.

For Engerix-B®

- **Expected (anticipated):** the event is identified in nature, severity, and frequency in the reference safety information in the U.S. product insert.
- **Unexpected (unanticipated):** the event is not identified in nature, severity, or frequency in the reference safety information in the U.S. product insert.

7.1.10 Suspected adverse reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

7.2 Methods and timing for assessing, and recording safety parameters

Unless specified otherwise all AE occurring between obtaining written subject's consent and subject's last study visit will be documented in the eCRF at all visits. All AE data and clinical laboratory data will be included in the study report.

Clinical investigators and ultimately the Site Principal Investigator have the primary responsibility for AE identification, documentation, grading, assignment of attribution and reporting to the sponsor.

7.2.1 AEs

All new AE or abnormal laboratory test values considered as clinically significant, expected or unexpected related or unrelated experienced after the subject has provided written consent should be recorded in the eCRF. AEs (any untoward medical occurrence in trial subject) do not necessarily have to have a causal relationship with treatment.

As a consistent method of collecting AEs, the subjects will be asked a non-leading question.

The investigator or delegates will record all directly observed AE, and all AE solicited or spontaneously reported by the subject, or reported in the subject's diary.

In addition to solicited AE following vaccination, unsolicited AE will be defined as follows: 1) AE, 2) serious AE (SAE), 3) medically significant event (condition prompting emergency room visit, physician visit not related to a common disease/not a routine visit or an SAE not related to a common disease), 4) investigator-determined new onset of chronic illness (NOCI). Any AE/SAE spontaneously reported at any study visit will be classified accordingly and reported in the eCRF.

AEs will be recorded in terms of medical diagnosis using the Medical Dictionary for Regulatory Activities (MedDRA). When this is not possible, the AE will be documented in terms of signs and symptoms observed by the investigator or as reported by the subject. In this case, each sign or symptom will be coded separately using MedDRA.

In addition, information provided for each AE will include: start date, treatment required if any assessment of the outcome at the time of reporting, causality, severity, and seriousness.

For each symptom the subject experiences, the subject will be asked if the subject received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

7.2.2 Vital signs and vaccine reactions

Vital signs will be assessed before and 30 minutes following each vaccination. Study subjects will be provided with a 28-day diary card to record vaccine reactions. Study subjects will be asked to record daily body temperature and local and systemic solicited adverse events on the day of vaccination and for the next 6 days. Study subjects will also be asked to record unsolicited adverse events in their diary card, on the day of vaccination and for the next 27 days. Vaccine reactions will be assessed at each visit and recorded in the eCRF for the corresponding visit. If a vaccine reaction meets the criteria of an SAE, the investigator or delegates will complete and submit an SAE report form (see also section SAE reporting).

For the recording of local vaccine reactions:

- The largest diameter of redness or swelling at the injection site will be measured and recorded daily on the day of vaccination and for the next 6 days in the eCRF.
- Subjects will be asked to indicate the maximum pain, tenderness and pruritus they experience at the injection site on a scale from 0 to 3 (0: no pain 1: Mild discomfort to touch 2: Discomfort with movement 3: Significant discomfort at rest) on the day of vaccination and for the next 6 days.

In addition, subjects will be asked to record local or general AE in the diary card that will be reviewed at each visit. AEs reported in the diary cards will be transcribed in English by the study center staff (if applicable) prior to recording in the eCRF. AEs transcribed to English from the diary card will be verified for accuracy during the site monitoring visit.

7.2.3 Laboratory test abnormalities

In subjects participating in the clinical laboratory sub-study, abnormal laboratory test values will be recorded individually in an AE form if they qualify as AE (see Section 7.1.5) and are not part of the data supporting a medical diagnosis already reported as an AE. Any Grade 4 potentially life-threatening laboratory abnormality (see Appendix 3) within 7 days after a study injection will stop any further study vaccinations in the subject, irrespective of the study vaccine relationship, as defined in Section 7.8.

7.2.4 SAEs, Medically Significant Event and New Onset of Chronic Illness

All SAEs, expected or unexpected, medically significant event and new onset of chronic illness occurring between the time the subject provides written consent and the last study visit will be documented in the eCRF, first in an AE form. For SAEs, upon completion of the AE form, and confirmation that the AE is an SAE, the investigator or delegate will be prompted to complete and submit a SAE report form. Follow-up SAE forms may be completed and submitted as needed e.g., if the event outcome, treatment and resolution are not known at the time of the initial report. The follow-up information should contain

sufficient detail to allow for a complete medical assessment of the case and an independent determination of possible causality, such as concomitant medications, or other conditions possibly explaining the SAE if any (must be consistent with the medical history recorded at baseline), relevant diagnostic tests, and autopsy report if applicable. All copies of source data attached with the SAE report form will be de-identified to protect subject subjects' privacy.

In addition, the reports should record: subject unique study ID, age, gender, weight, initial or follow-up report, date of the event, date of report, and individual completing the report.

7.3 Expedited reporting procedures to study sponsor and pharmacovigilance agent

7.3.1 Serious Adverse Events

SAEs require prompt or immediate reporting to the site Principal Investigator or designates. The site Principal Investigator will be responsible for reporting the SAEs to study sponsor/pharmacovigilance agent as per protocol, and to the IRB/REB if/as required by institutional policies and procedures.

The site Principal Investigator or delegates will complete and submit a SAE form in the eCRF, within 24 hours of becoming aware of the SAE. An E-mail notification of the SAE will be sent automatically to the Medical Monitor/pharmacovigilance agent appointed by study sponsor. The Medical Monitor/pharmacovigilance agent will assess the SAE report and proceed to report to the appropriate regulatory bodies as described in section 7.4.

Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

7.3.2 Reporting of pregnancy

Female subjects, if of child-bearing potential are required to use adequate contraception methods as part of the entry criteria.

If any study subject becomes or is found to be pregnant during the treatment period or within 4 weeks of the last injection of study vaccines, the pregnancy will be reported in the same way as SAEs to study sponsor using the SAE Report Form, including an estimated date of conception (EDC), and the date of last study vaccine dose. Pregnancies will be followed by the investigator until completion of the pregnancy to learn the outcome, as congenital anomaly/birth defect is a SAE. Spontaneous abortion, ectopic pregnancy and stillbirth will also be considered as a SAE. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to the study sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

7.4 Reporting to regulatory authorities

The study sponsor (or delegate) will report any unexpected fatal or life-threatening suspected adverse reactions to the appropriate regulatory authorities as soon as possible but no later than 7 calendar days of initial receipt of the information.

The study sponsor is also responsible for reporting to the appropriate regulatory authorities and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting, any:

- suspected adverse reaction that is both serious and unexpected, reported by any study center irrespective of the location.

- suspected adverse reaction that is both serious and unexpected occurring in any of the subjects of the clinical trial, which are identified by or come to the attention of the sponsor after the end of the clinical trial
- findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

If the regulatory authority requests any additional data or information, the study sponsor (or delegate) must submit it as soon as possible, but no later than 15 calendars days after receiving the request.

The study sponsor (or delegate) will submit periodic reports of the progress of the trial, if and as, requested by the regulatory authorities.

7.5 Institutional Reporting of AEs and SAEs

The investigator will be responsible for reporting all SAEs directly to the relevant ethical review body (IRB/REB) according to institutional policies.

In addition, the investigator will be responsible for reporting AEs directly to the relevant ethical review body (IRB/REB) if and as requested by institutional policies, and will also provide the ethical review body with any safety reports prepared by/on behalf of the study sponsor.

7.6 Type and duration of follow-up of subjects after AEs

All AEs and SAEs will be followed until they are resolved (return to normal or baseline values), unless: 1) they are judged by the investigator to be no longer clinically significant, 2) the investigator attributes the AE/SAEs to a cause other than the study drug or assesses them as chronic or stable, or 3) the subject is lost-to follow-up. Supplemental measurements and/or evaluations may be necessary to fully investigate the nature and/or causality of an AE or SAE. This may include laboratory tests, diagnostic procedures or consultation with other healthcare professionals. If the subject dies, any post-mortem findings (including histopathology) must be provided to the Sponsor or designee. In addition, the designated Medical Monitor may request blood tests, diagnostic imaging studies or specialist physician consultations in order to further evaluate any AE or abnormality considered to be potentially clinically significant.

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

7.7 Unblinding

The blind should ordinarily be broken for regulatory submission.

When reporting a Suspected Unexpected Serious Adverse Reaction (SUSAR) to regulatory authorities the sponsor shall only unblind the treatment allocation of the affected subject to whom the SUSAR relates.

If an event is potentially a SUSAR the blind shall be broken for that subject only by the sponsor. The blind shall be maintained for other persons responsible for the ongoing conduct of the clinical trial (such as the management, monitors, investigators) and those persons responsible for data analysis and interpretation of results at the conclusion of the clinical trial, such as biometrics personnel.

Unblinded information shall be accessible only to persons who need to be involved in the safety reporting to regulatory authorities, to the data monitoring committee, or to persons performing ongoing safety evaluations during the clinical trial.

Unblinding of sites in case of an emergency is not anticipated in this study since it is very unlikely that the knowledge of the vaccine or vaccine lot received by the subject will affect his/her medical management.

The investigator may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. The unblinding should be formally completed in IWRS. Whenever possible, the investigator must first discuss options with the Study Medical Monitor or appropriate VBI study personnel **before** unblinding the subject's treatment assignment in IWRS. If this is impractical, the investigator must notify the Contract Research Organization (CRO) and sponsor as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool. If the Investigator does not have access to IWRS or is having technical issues, investigator can contact unblinded staff at the site for the treatment but this must be clearly documented in the source notes and should only be used as a back-up option.

For all other cases, the Medical Monitor will determine on a case-by-case basis if it is necessary to break the blind for safety purposes. The blind will be broken by the Medical Monitor or his designee for the specific subject. In the event that the blind is broken for a subject, the blind will be maintained for the clinical study team members to the extent possible to minimize the potential for introducing bias in evaluating the subject's data.

7.8 Stopping Rules

Stopping criteria for further study vaccinations in individual subjects:

The investigator will notify the sponsor (and/or sponsor representative) if any of the below conditions occur and will stop any further study vaccinations in an individual subject if they experience any of the following:

- Grade 4* post-injection reaction within 7 days after any study injection
- Clinically significant systemic reaction (i.e., angioedema, generalized urticaria) within 7 days after any study injection
- Grade 3 or 4* hypotension within 24 hours after any study injection
- Grade 3 or 4* respiratory reaction occurring within 24 hours after any study injection
- Grade 4** potentially life-threatening laboratory abnormality within 7 days after a study injection, irrespective of the study vaccine relationship (in clinical laboratory sub-study subjects)
- Any life-threatening event within 7 days after any study injection, regardless of relationship to study vaccine

*FDA Grading of Vaccine Reactions and FDA Grading of Vital Sign Abnormalities (Appendix 2)

**FDA Grading of Clinical Laboratory Abnormalities (Appendix 3)

7.9 Safety oversight

An independent Data Monitoring Committee (DMC) for this study will monitor human subject safety and consider study-specific data as well as relevant background information about the study vaccines, and target population under study.

The DMC will comprise of a minimum of 3 members. The DMC will operate under procedures that will be developed at the organizational meeting of the DMC. At this time, each data element that the DMC needs to assess will be clearly defined. The DMC will meet before the study starts or as soon thereafter as possible to discuss the protocol, set triggers for data review, define a quorum, establish guidelines for monitoring the study, and designate a DMC Chair, and then as often as necessary.

All discussions and decisions will be documented in writing. The DMC will advise the study sponsor of its findings in writing.

In the event that a stopping rule for an individual subject is triggered (Section 7.8), the data monitoring committee will meet on an ad hoc basis to review the data and determine whether the clinical trial should be stopped or requires modification in order to proceed safely.

The DMC will only meet if a stopping rule for an individual subject is triggered. In the event that a stopping rule is triggered, the DMC will make every reasonable attempt to meet as soon as possible, preferably within three (3) to five (5) business days of the Sponsor being notified of the event, but no later than ten (10) business days. During this period, the DMC will be provided the relevant information regarding the event(s) that triggered the stopping rule for the subject.

In the event that adequate information is not available in the timeframe noted above, the DMC may schedule a second meeting to review additional information regarding the event(s) triggering a stopping rule in an individual subject.

8 MONITORING

Study center monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by a CRO appointed by the study sponsor. Details of clinical site monitoring will be documented in the Clinical Monitoring Plan (CMP) developed by the CRO and approved by the study sponsor.

The monitor will ensure that all subjects have been enrolled according to the protocol and that informed consent has been obtained prior to any study procedure. Monitors will review the study files, the subject files, source documents, eCRF, any SAE forms, as well as the product logs and laboratory records to ensure that the study is being conducted according to the protocol and GCP. eCRFs will be reviewed according to the defined monitoring plan.

The study will be monitored once the first subject has been enrolled, during the study at appropriate intervals, and after the last subject has completed the study. The monitoring visit schedule will be determined by the monitor and investigator, based on the frequency of enrollments and follow-up visits.

Audits and inspections may be conducted by the relevant ethical body or regulatory authorities and to ensure that the study is conducted in accordance to the protocol, and applicable ethics norms, ICH GCPs, and all applicable regulations.

9 STATISTICAL CONSIDERATIONS

The statistical analysis of the data obtained from this study will be the responsibility of the designee of the sponsor.

The statistical considerations summarized in this section outline the plan for data analysis of this study. If, after the study has begun, but prior to any un-blinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 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 $\log_{10}$(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%

9.2 Randomization

This is a double blind 4-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. 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.

9.3 Analysis Sets

9.3.1 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.

9.3.2 Safety Set

All subjects in the All Enrolled Set who receive a study vaccination.

9.3.3 Full Analysis Set (FAS)

All subjects in the All Enrolled Set who receive at least one vaccination and provide at least one evaluable serum sample both before and after baseline. The FAS will be analyzed "as randomized" (i.e., according to the vaccine a subject was randomized to receive, which may be different from the vaccine the subject actually received). A FAS will be defined for each relevant time point.

9.3.4 Per Protocol Set (PPS)

All subjects in the FAS who:

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

A major protocol violation for the purpose of exclusion from the PPS is defined as a protocol violation 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 visits outside the allowed windows
- Subjects who developed withdrawal criteria but were not withdrawn
- Subjects who received a prohibited concomitant medication that is judged to impact the reliability of subject immunogenicity results
- Subjects with a deviation identified through monitoring visits or otherwise, where the deviation is judged to impact the reliability of subject immunogenicity results

9.3.5 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 and ethnicity

9.4 Analysis of Demographic and Baseline Characteristics

All demographic and baseline characteristics will be 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. Data will be summarized by Sci-B-Vac™ lot, Sci-B-Vac™ treatment group and Engerix-B® treatment group.

9.5 Primary Objective

9.5.1 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-HBs ratios 4 weeks after the third injection, 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]

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

9.5.2 Statistical Methods for Primary Immunogenicity Analysis

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, the primary immunogenicity analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

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

All statistical analyses will be performed on the logarithmically (base 10) transformed values. Individual titers below the detection limit will be set to half the limit.

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, anti-HBs 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 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), 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, then manufacturing equivalence (lot-to-lot consistency) will be demonstrated. If consistency is demonstrated, then the data from the three lots will be combined to address the secondary immunogenicity non inferiority-hypothesis.

9.6 Secondary Objective

9.6.1 Secondary Hypothesis

If the primary hypothesis test is successful, the secondary hypothesis will be tested. The secondary hypothesis is 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®. Seroprotection is defined as anti-HBs levels ≥ 10mIU/mL in serum. Seroprotection rate (SPR) is the percentage (%) of subjects achieving seroprotection.

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 the third vaccination, will be > - 5%."

The analysis will use a two-sided 5% significance level. The PPs will be used to test the secondary hypothesis.

9.6.2 Statistical Methods for Secondary Immunogenicity Analysis

For the secondary endpoint of SPR at day 196, 4 weeks following the third vaccination, data from all centers will be pooled and data from all 3 lots of Sci-B-Vac™ will be pooled. The difference in proportions and two-sided 95% CIs, will be calculated using the Miettnen and Nurminen method. For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, this primary analysis will comprise a complete case analysis only without introducing any bias. Imputation methods will not be used. This analysis will use the PPS.

The impact of center will be investigated through funnel plots.

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

9.7 Exploratory Analyses

Analysis of all exploratory immunogenicity endpoints will be based on the PPS, unless otherwise indicated. No adjustment for multiplicity will be made. All analyses will comprise a complete case analysis only. Data from all centers will be pooled.

The following exploratory immunogenicity endpoints will be summarized:

- 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.
- 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.
- Proportion of subjects achieving anti-HBs levels ≥ 100mIU/mL in serum, 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.

- 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.
- 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®.

Each of the above endpoints 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 Miettnen and Nurminen method.

In addition, each of the above 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 Miettnen and Nurminen method.

9.8 Analysis of Safety Objectives

There are no statistical hypotheses associated with the safety objectives. All safety data will be analyzed using descriptive statistics. For all safety summaries, 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 to allow for comparisons. All safety analyses will be presented using the Safety Analysis Set.

9.8.1 Analysis of Extent of Exposure

The number of subjects actually receiving the first, second and the third vaccination will be summarized by Sci-B-Vac™ lot, Sci-B-Vac™ treatment group and Engerix-B® treatment group.

9.8.2 Analysis of Solicited Local, Systemic and Other Adverse Events

All solicited AEs will be summarized according to defined severity grading scales. 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) 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) - see Appendix 2. Frequencies and percentages of subjects experiencing each AE will be presented by treatment group for each symptom, overall and by dose and severity, for each age group and by time point (i.e., after each vaccination).

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 overall by time point (i.e., after each vaccination). 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:

- SAEs
- Unexpected AEs
- AEs that are very likely, probably or possibly related to vaccine
- AEs of special interest
- AEs leading to vaccine/study withdrawal

9.8.3 Analysis of Vital Signs and Laboratory Parameters

All vital sign data and laboratory (e.g., hematology, chemistry) data (clinical laboratory sub-study) 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 Appendix 2 for vital signs and Appendix 3 for laboratory parameters.

9.9 Planned Interim Report

Not applicable

10 DATA HANDLING AND RECORD KEEPING

Data handling, record-keeping, reporting, study record retention and protocol deviations will be managed in accordance with FDA regulations and ICH GCP and will be described in detail in study-specific SOPs.

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is recommended to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained

Study sponsor and/or it designee will provide guidance to investigators on making corrections to the source documents and eCRF.

10.1 Data management responsibilities

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality, and reviewed by the site Principal Investigator or designee.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

10.2 Data capture methods

Clinical data (including AEs, concomitant medications, and reactogenicity data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant eCRF. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.3 Types of data

Data for this study will include safety (vital signs, clinical signs and symptoms, concomitant medications and clinical laboratory tests), and efficacy outcome measures (immunogenicity).

10.4 Study records retention

Following closure of the study, the investigator must maintain all center study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g., audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

The investigator/institution should seek the written approval of the Sponsor before proceeding with the disposal of these records after the indicated time period for record retention.

The minimum retention time will meet the strictest standard applicable to a particular study site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, including national laws governing the archiving of medical files of subjects; otherwise, the minimum retention period will default to 25 years after the end of the clinical trial.

The investigator/institution must notify the Sponsor of any changes in the archival arrangements, including, but not limited to, archival at an off-study site facility, transfer of ownership of the records in the event the investigator leaves the study site.

10.5 Protocol deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3 5.1.1 Quality Assurance and Quality Control, Section 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations to the local Trial Coordinator within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the study sponsor or its designees according to the study manual of operating procedures.

All deviations from the protocol must be addressed in study subject source documents. A Protocol Deviation Form should be completed in the eCRF. Protocol deviations must be reported to the relevant ethical body to institution policies. The site PRINCIPAL INVESTIGATOR /study staff is responsible for knowing and adhering to their institution policies.

11 QUALITY CONTROL AND QUALITY MANAGEMENT

Standard Operating Procedures (SOPs) for quality management will be developed, used to train appropriate personnel, and kept on file with documentation of training. Data will be evaluated for compliance with protocol and accuracy in relation to source documents. The study will be conducted in accordance with procedures identified in the protocol. The types of materials to be reviewed, the personnel responsible, and the schedule for reviews will be referenced in the SOPs. Study-specific training will be provided for all staff prior to the commencement of the trial.

SOPs will be used at all clinical and laboratory sites. Regular monitoring and an independent audit will be performed according to GCP/ICH (e.g., data monitoring). Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Reports will be submitted to study sponsor on monitoring activities.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the study sponsor, and inspection by local and regulatory authorities.

The Data Management Center will implement quality control procedures according to the data management plan, beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

12 STUDY REGISTRATION AND RESULTS INFORMATION

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trial registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine.

It is the responsibility of study sponsor to register this trial in ClinicalTrials.gov before any subject enrolment and to comply with the requirements for the submission of results information as per US 42 CFR Part 11 [Clinical Trials Registration and Results Information Submission].

The sponsor will register the trial in the EudraCT database, which shares information with the publicly available European Union Clinical Trial Register and will comply with applicable regulations and guidelines with respect of the posting of results-related information.

13 ETHICAL / REGULATORY CONSIDERATIONS

13.1 Relevant ethical body

A relevant ethical body is either and Institutional Review Board (IRB) or an Independent Ethics committee (IEC).

An Independent Ethics committee is:

> An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.
>
> The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but an Independent Ethics Committee should act in agreement with ICH Good Clinical Practice guidance document.

An Institutional Review Board (IRB) is:

> An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

It is the responsibility of the site Principal Investigator to identify the relevant ethical body that has the responsibilities described in the Section 3 of the ICHGCP with respect of trials conducted at the site.

Note: There could be more than one relevant ethical body e.g. If the Principal Investigator has a cross appointment with a hospital and a university and both institutions require the trial to be reviewed by their respective ethics committees. In that case, it the Principal Investigator's responsibility to identify all the relevant ethical bodies. The singular form will be used in this document for simplification purposes. However it should be understood that if more than one ethical body has the responsibilities described in the section 3 of the ICHGCP with respect of clinical trials conducted at the site, then all obligations /procedures described in this section and in Sections 7, 8 and 10.5 of this protocol apply for all relevant ethical bodies.

13.2 Ethics Review and informed consent

The Principal Investigator or designate will be responsible for presenting a full description of the research project including risks/benefits and how personal health information may be used and disclosed in research. A written informed consent/authorization will then be obtained from the subject prior to the screening procedures and injection. The Principal Investigator or designate will also be responsible for maintaining up-to-date records of the consent forms and providing a copy to the subject.

Subjects will be encouraged and will have ample opportunity to have their questions answered before and after consenting to participate.

The Principal Investigator must receive a copy of the letter of approval from any relevant ethical body, which specifically approves the protocol and informed consent, before beginning or continuing subject enrollment.

The relevant ethical body must also approve any significant changes to the protocol and documentation of this approval must be sent to the Principal Investigator.

Records of all study review and approval documents must be kept on file by the Principal Investigator and are subject to inspection by regulatory authorities during or after completion of the study. SAEs must be reported to the relevant ethical body. Other AEs should be reported according to modalities defined in the ethical body policies and procedures. The relevant ethical body should receive notification of completion of the study and final report within 3 months of study completion and termination. The Principal Investigator will maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted.

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15 APPENDICES

15.1 Appendix 1: Schedule of Events

	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.

15.2 Appendix 2: FDA guidelines for grading vaccine reactions

Table 2: 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.*

Table 3: Grading of vital signs abnormalities

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	39.0 – 40 102.1 – 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.*

Table 4: Systemic reactions

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

15.3 Appendix 3: FDA guidelines for grading clinical laboratory abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Conversion factors to SI units will be provided to the clinical sites.

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1–10 xULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

** The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate. ** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125-129 mEq/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.*

****ULN is the upper limit of the normal range.*

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

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

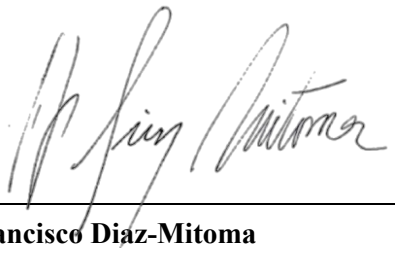
Version	Version Date	Author	Summary of Changes Made
Draft 1.0	16May2017	Yongmei Zhou (Biostatistician)	New Document
Final 1.0	See Footer	Yongmei Zhou (Biostatistician)	1. Delete age derivation since date of birth is collected as MMYYYY 2. Wording to match protocol 3. Updated based on protocol version 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	

Document prepared and approved by:

Brian Mangal, M.Sc.	**Date (DD Mmm YY)**
Senior Director, Biostatistics	

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:

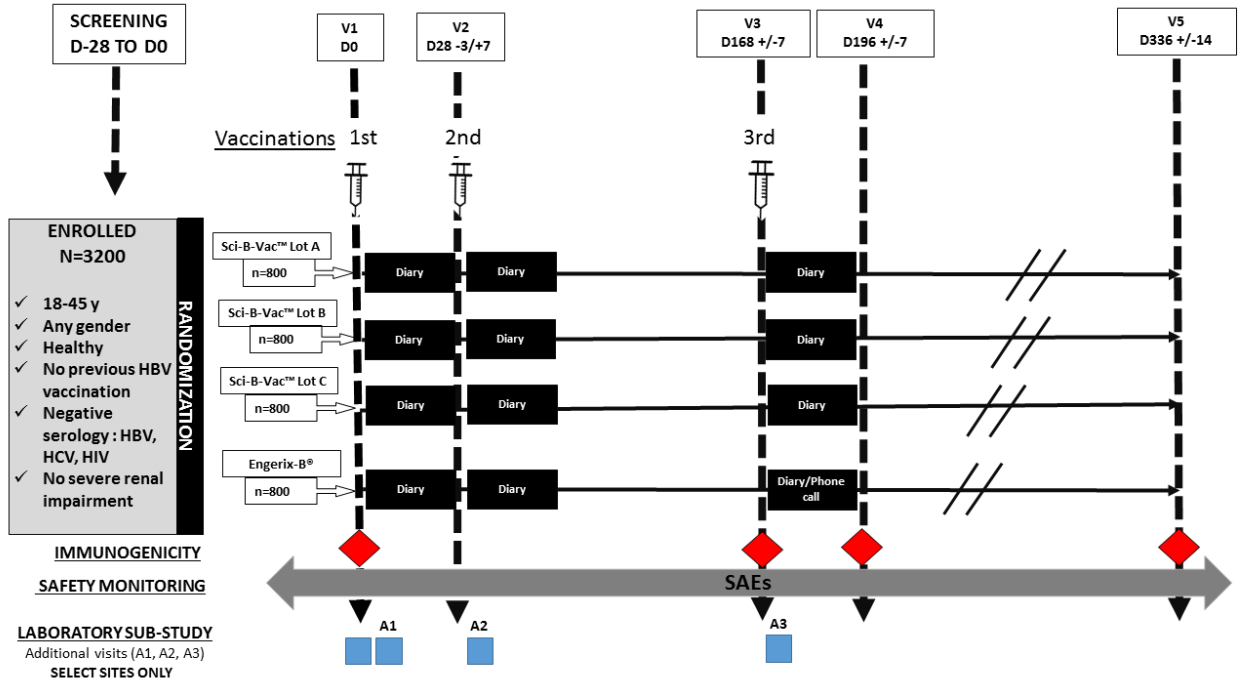
- To assess the Geometric Mean Concentration (GMC) of anti-HBs in serum after 2 vaccinations, just prior to receiving the third vaccination, and 24 weeks after the third vaccination with Sci-B-Vac™ or Engerix-B®, on Study Days 168 and 336, respectively.
- To assess the seroprotection rate after 2 vaccinations, 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