STUDY PROTOCOL

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

Protocol Identifying Number: Sci-B-Vac–001

NCT Number: NCT03393754

Version: 2.0, Amendment 1

Date of Version: July 17, 2017

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

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Confidentiality Statement

Sponsor Signature Page

Sponsor Signatory:

	21/07/2017
Francisco Diaz-Mitoma	Date (dd/mm/yyyy)

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List of abbreviations

aa: amino acid
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
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.
EEA: European economic area
EPO: erythropoietin
E.U.: European union
FAS: full analysis set
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
HBA1C: Hemoglobin A1C
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

ITT: intent-to-treat
IWRS: interactive web response system
LLN: lower limit of normal range
MCAR: missing completely at random
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
NOCI: new onset of chronic illness
PPS: per protocol set
SAE: serious adverse event
SBP: systolic blood pressure
DMC: data monitoring committee
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: whilte blood cell 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 the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Any change to the protocol that affects subject selection, safety, or changes in the conduct of the trial will require written approval from the IRB/IEC 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 IRB/IEC 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

Long Title	A Phase 3 Double-Blind Randomized Controlled Trial to Compare the Immunogenicity and Safety of a Three-dose Regimen of Sci-B-Vac™ to a Three-dose Regimen of Engerix-B® in Adults
Clinical Trial Phase	3
Study sponsor	VBI Vaccines Inc.
Number of sites	~ 30 sites (Canada, Europe, United States)
Background & Rationale	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 hepatitis B virus (HBV) worldwide[1]. In 2013, it is estimated that 686,000 people of all ages died of 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 is 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. The 1 mL dose of Engerix-B® containing 20 µg of HBsAg is the form 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 vaccination, 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 current study is being undertaken 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 antigen adsorbed onto 0.5 mg of aluminum as aluminum hydroxide, sodium chloride, potassium chloride, disodium hydrogen phosphate dodecahydrate, potassium dihydrogen phosphate anhydrous and water for injection. ACTIVE COMPARATOR: Engerix-B® (1.0 mL single dose vials) 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 study is a double-blind randomized controlled trial designed to establish the non-inferiority of Sci-B-Vac™ compared to Engerix-B® in adults ≥ 18 years old. Study subjects will be randomized 1:1 via a web-based system to receive either a total of 3 injections of Sci-B-Vac™ or 3 injections of Engerix-B® intra-muscularly (IM) (one injection on Study Day 0, one injection at 4 weeks (on Study Day 28) and one injection at 24 weeks (on Study Day 168)). Randomization will be stratified by study center, and age (18-44 years, 45-64 years and ≥ 65 years). There will be targeted enrollment to the ≥ 45 year old age groups, to ensure adequate power to establish superiority of Sci-B-Vac™ in adults ≥45 years old (co-primary objective) according to the parameters detailed in Section 9.5.1 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 6 visits (denoted V1, V2, V3, V4, V5, and End of Study visit, V6). 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 dose.

	Each subject will receive one injection of 1 mL of Sci-B-Vac™ or Engerix-B® 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. 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. Immunogenicity will be assessed at baseline (Study Day 0) and on Study Days 28, 56, 168, 196 and 336. Immunogenicity endpoints will be evaluated using a validated quantitative hepatitis B surface antibody [anti-HBs] test (see below primary endpoint). Anti-pre-S1 and anti-pre-S2 investigations will be exploratory. Safety evaluations will include standardized methods for local and systemic vaccine reactions, repeated vital signs and physical examinations, 48 weeks 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. From this clinical laboratory sub-study, ~n=50-75 subjects /treatment arm will also be enrolled in an optional sub-study on cell-mediated immunity. 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	The total sample size is 1,564 subjects (782 per arm). Targeted enrollment by age strata will be as follows: Age 18-44 years (20%): 312 (~ 156 per arm) Age 45-64 years (40%): 626 (~313 per arm)

	Age ≥ 65 years (40%): 626 (~313 per arm) Enrollment within each stratum will be stopped once the target has been met.
Study Population:	Subjects meeting all the inclusion criteria and none of the exclusion criteria below. **Inclusion criteria** 1. Any gender. 2. Age ≥ 18 years. 3. In stable health as determined by a physical examination and laboratory tests values. Common chronic conditions such as, but not limited to, type 2 diabetes, high blood pressure, COPD and asthma will be accepted if the condition is well controlled, as determined by the investigator, **and** not meeting the exclusion criteria. For subjects > 65 years old, Frailty Index ≤3 [17](see Appendix 1). 4. If female: a) either is not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), OR b) is of childbearing potential and must agree to use an adequate birth control method during the screening period and until the end of her participation in the study (effective birth control includes: 1) hormonal (implant, oral, vaginal, transdermal) contraceptives; 2) diaphragm with spermicide, condom (with or without spermicide); 3) intra-uterine devices; and 4) vasectomy of male partner; 5) abstinence from penile-vaginal intercourse (if the preferred and usual lifestyle of the subject)). 5. Able and willing to give consent. **Exclusion criteria** 1. Previous vaccination with any HBV vaccine (licensed or experimental). 2. Treatment by immunosuppressant within 30 days of enrollment including but not limited to corticosteroids at a

	dose that is higher than an oral or injected physiological dose, or a prednisolone-equivalent dose > 20 mg /day (Inhaled and topical steroids are allowed). 3. Known history of immunological function impairment, including but not limited to: a) autoimmune diseases (e.g., multiple sclerosis, type 1 diabetes, myasthenia gravis, Crohn disease and other inflammatory bowel diseases, celiac disease, systemic lupus erythematosus, scleroderma, including diffuse systemic form and CREST syndrome, systemic sclerosis, dermatomyositis polymyositis, rheumatoid arthritis, juvenile idiopathic arthritis, autoimmune thyroiditis -including Hashimoto thyroiditis, Grave's or Basedow's disease, immune thrombocytopenic purpura, autoimmune hemolytic anemia, autoimmune hepatitis, psoriasis, vitiligo, vasculitis, Guillain-Barré syndrome, Addison's disease, Bell's palsy and alopecia areata); OR b) secondary immunodeficiency disorders (e.g. resulting from HIV/AIDS (Acquired Immunodeficiency Syndrome caused by Human Immunodeficiency Virus infection), solid organ transplant, splenectomy); OR c) primary immunodeficiency disorders (e.g. common variable immune deficiency (CVID), Defective phagocytic cell function and neutropenia syndromes, complement deficiency). 4. Pregnancy or breastfeeding. 5. Immunization with attenuated vaccines (e.g. MMR) within 4 weeks prior to enrollment. 6. Immunization with inactivated vaccines (e.g. influenza) within 2 weeks 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 (Engerix-B® or Sci-B-Vac™). 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 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) $\leq$60 mL/min/1.73m^2 at screening 19. Uncontrolled diabetes mellitus (defined as HbA1C >8.5%). 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. Any laboratory test abnormality that would be considered of Grade 1 severity or above as per Appendix 4 **and** is considered as clinically significant by the investigator. Grade 3 severity or above is exclusionary, regardless of clinical assessment. 22. Diagnosis of advanced stage heart failure (New York Heart Association (NYHA) class III or IV – see Appendix 5) or Unstable Angina.
Study Duration	15-18 months (recruitment + 12 months 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 Objectives	Co-Primary Objectives: • 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® in adults ≥18 years old; 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%. **And** • To demonstrate that the SPR 4 weeks after completion of the three-dose regimen of Sci-B-Vac™ is superior to a three-dose regimen of Engerix-B® in adults ≥ 45 years old i.e. the lower bound of the 95% two-sided CI of the difference between the SPR in the Sci-B-Vac™ arm minus the SPR in the Engerix-B® arm, achieved 4 weeks after the third vaccination, will be >5%.
Secondary Objectives	• To determine whether the SPR after 2 vaccinations with Sci-B-Vac™, evaluated 4 weeks and 20 weeks after the second vaccination (just prior to receiving the third vaccination), is

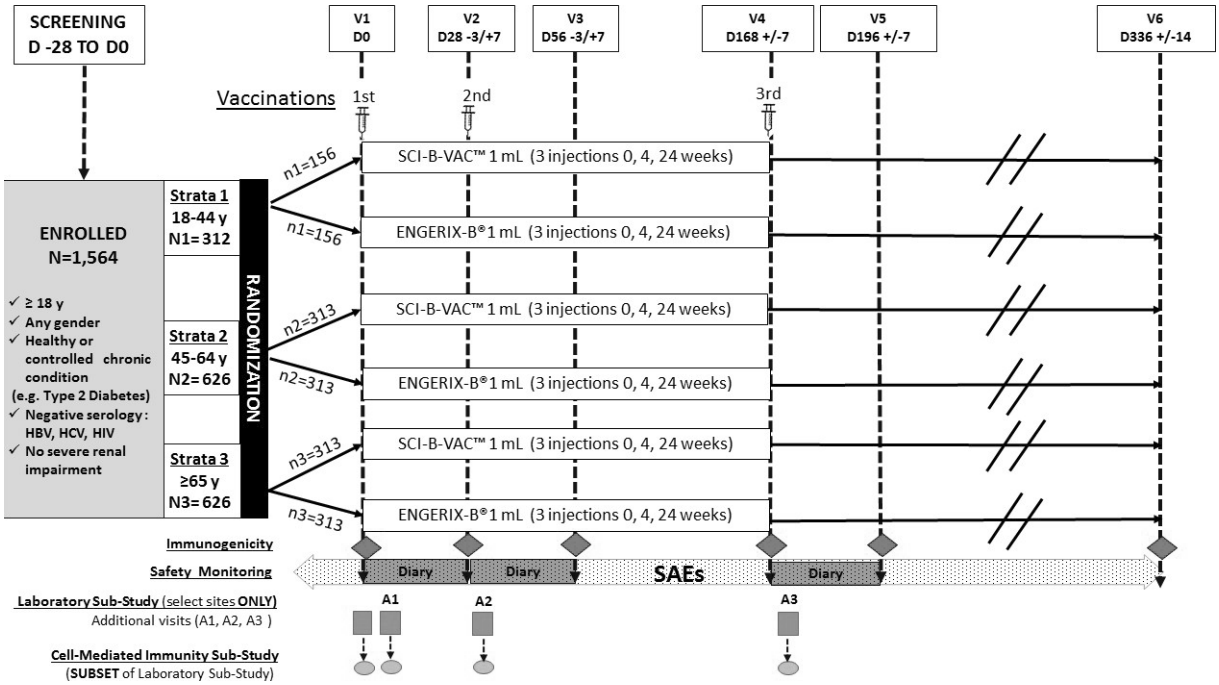
	non-inferior to the SPR 4 weeks after receiving the third vaccination with Engerix-B®. • To compare the safety and reactogenicty of Sci-B-Vac™ and Engerix-B®.
Exploratory Objectives	• To compare the geometric mean concentration (GMC) of anti-HBs, 4 weeks after receiving the first vaccination, second vaccination and third vaccination, 20 weeks after receiving the second vaccination (just prior to receiving the third vaccination), and 24 weeks after receiving the third vaccination with Sci-B-Vac™ or Engerix-B®. • To compare the SPR 4 weeks after receiving the first vaccination and second vaccination, 20 weeks after receiving the second vaccination (just prior to receiving the third vaccination), and 24 weeks after receiving the third vaccination with Sci-B-Vac™ or Engerix-B® on Study Days 28, 56, 168 and 336. • To compare the proportion of subjects who achieve anti-HBs levels ≥ 100 mIU/mL, as a measure of an especially robust immune response, 4 weeks after each vaccination with Sci-B-Vac™ or Engerix-B®, on Study Days 28, 56, and 196 and on Study Days 168 and 336. • To compare the rate of non-response (defined as the proportion of subjects not attaining anti-HBs levels ≥ 10 mIU/mL) 4 weeks after receiving the third vaccination with Sci-B-Vac™ or Engerix-B®. • To assess the antibody responses against Pre-S1 and Pre-S2 at baseline, 4 weeks after each vaccination with Sci-B-Vac™ or Engerix-B®, and at day 168 and 336. • To compare SPR, GMC and rate of non-response in subgroups of interest (e.g. BMI>30), 4 weeks after receiving the third vaccination with Sci-B-Vac™ or Engerix-B®. • To compare clinical laboratory parameters relative to baseline 1 week after each vaccination with Sci-B-Vac™or Engerix-B® in a subset of subjects (at least 10% of the total number of subjects enrolled to the trial).

	• To compare the boost relative to baseline of the cell-mediated immune response, 1 week after receiving each vaccination with either Sci-B-Vac™ or Engerix-B®, in a small subset of subjects (~50-75 subjects/treatment arm).
Primary endpoint	• Seroprotection rate (SPR) achieved on Study Day 196, 4 weeks post-third vaccination with either Sci-B-Vac™ or Engerix-B®. Seroprotection is defined as anti-HBs levels ≥ 10 mIU/mL in serum. Seroprotection rate is the percentage (%) of subjects achieving seroprotection.
Secondary Endpoints	• SPR, 4 weeks and 20 weeks after receiving the second Sci-B-Vac™ vaccination (just prior to receiving the third vaccination), and SPR 4 weeks after receiving the third Engerix-B® vaccination. • Number (%) of subject-reported, solicited (on the day of vaccination and during the next 6 days), unsolicited adverse events (AE) (on the day of vaccination and during the next 27 days), and number (%) of SAEs, medically significant events 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 and/or physical examination findings, compared to baseline.
Exploratory endpoints	• Geometric Mean Concentration (GMC) of anti-HBs in serum, at baseline and 4 weeks after each vaccination with either Sci-B-Vac™ or Engerix-B® i.e. on Study Days 28, 56, and 196, and 20 weeks after receiving the second vaccination (just prior to receiving the third vaccination) on Study Day 168 and 24 weeks after receiving the third vaccination, and on Study Day 336. • SPR in both study arms at baseline and on Study Days 28, 56, 168 and on Study Day 336. • Proportion of subjects achieving anti-HBs levels ≥100mIU/mL in serum, 4 weeks after each vaccination with

	either Sci-B-Vac™ or Engerix-B®, on Study Days 28, 56, and 196, and on Study Days 168 and 336. • Rate of non-response on Study Day 196 (defined as the proportion of subjects not attaining anti-HBs levels ≥ 10 mIU/mL on Study Day 196), 4 weeks after receiving the third vaccination with either Sci-B-Vac™ or Engerix-B®. • Geometric Mean Concentrations (GMC) of anti-pre S1 antibody and anti pre S2 antibody in serum at baseline and 4 weeks after each vaccination with Sci-B-Vac™ or Engerix-B® on Study Days 28, 56, and 196, and on Study Days 168 and 336. • 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). • Cell-mediated immunity against HBs at baseline, 1 week after each vaccination with either Sci-B-Vac™ or Engerix-B® (on a small subset of subjects enrolled in the clinical laboratory sub-study).

SCHEMATIC OF STUDY DESIGN

Figure 1: Schematic of Study Design



PROTOCOL AMENDMENTS Sci-B-Vac-001

Protocol Version	Issue Date
Original Protocol	5 May 2017
Amendment 1	17 July 2017

Amendment 1 (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 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 under 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" and Section 4.1 "Subjects Population"	Number of sites has been changed from 30-45 to ~ 30 sites.
Rationale: Fewer sites are required than initially expected, given the recruitment potential at participating sites.	
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"

Rationale: Clarification on the amount of aluminum per 1 mL in the aluminum hydroxide adjuvant.	
Protocol Summary and "Study Design"	Change made to reflect that clinical laboratory assessments will be carried out in study subset (at least 10% of the total number of subjects enrolled to the trial) throughout the full three-dose regimen, 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 "Study Design"	Clarification made that subjects invited to participate in the optional sub-study of cell-mediated immunity will be recruited from subjects already participating in the clinical laboratory sub-study (select sites).
Rationale: To clarify that only subjects at select sites will contribute to the clinical laboratory sub-study and be eligible to participate in the optional sub-study on cell-mediated immunity sub-study.	
Protocol Summary "Exclusion criteria" #2 and Section 4.1.2	"within 30 days of enrollment" has been added to exclusion criteria #2.
Rationale: This clarification was made to exclude subjects that have recently received immunosuppressants from being enrolled to the study, as this may affect response to vaccination.	
Protocol summary, "Exclusion criteria" #20 and Section 4.1.2 "Exclusion criteria"	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 "Study Duration"	Longer study duration listed.
Rationale: To account for a potentially longer study recruitment period.	
Protocol Summary – "Exploratory Objectives" and Section 2.3 "Exploratory Objectives"	Clarification provided to distinguish between the clinical laboratory exploratory objectives and the exploratory objectives of the cell-mediated immune response sub-study. Study Days are also now provided for clarity for the SPR comparisons, 4 weeks post vaccination.

Rationale: To delineate the specific exploratory objectives and to clarify the timing of exploratory comparisons of interest.	
Protocol Summary – "Exploratory Endpoints" and Section 3.4 "Exploratory Endpoints"	Addition of SPR exploratory endpoint for consistency with exploratory endpoints defined in Section 3.4. Also, separation of cell-mediated immune response endpoint and clinical laboratory parameter endpoint, for clarity.
Rationale: Changes made to ensure consistency within the document.	
Protocol summary – "Exploratory Objectives" 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).	
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 assessments at Day 0 and 7 days after each vaccination. Clarification is also provided on the number of visits and evaluations required for the main study and separately for the laboratory sub-study and the sub-study of cell-mediated immunity.

Rationale: To improve clarity and consistency within the protocol and to accurately present the main study visits (V1-V6) and the additional clinical laboratory visits (A1-A3) for select sites participating in the clinical laboratory sub-study.	
Sections 3.1, 6.2.4, 6.3.2, 6.3.5 and 6.3.7	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 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: Given the age of the population being enrolled, 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	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. Safety laboratory Visit 2 in the main study has been replaced with a telephone follow up, 7 days after the first vaccination.
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 update the 7-day telephone follow up after the first 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 vaccine.
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 6.2.3 "Safety laboratory evaluations"	Section 6.2.3 has been removed and replaced with new section 6.2.4.1 "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 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).	
Section 6.2.4.2 – "Optional sub study of cell-mediated immunity"	Modifications made to the text to reflect that subjects enrolled to the cell-mediated sub-study will be recruited from the clinical laboratory sub-study. Clarification is also provided in the text that these sub-studies will include 3 additional assessments (A1, A2, A3), one week after each vaccination.
Rationale: To clarify the enrollment procedures and sub-study requirements for the laboratory and cell-mediated immunity sub-studies.	
6.2.5 "Biological samples, handling, analysis and storage"	Changes made to reflect new sample requirements for clinical laboratory assessments and the optional cell-mediated immunity sub-study, one week after each vaccination. Subjects in the clinical laboratory sub-study will be required to come for 3 additional visits (A1, A2, A3) and provide 4 additional blood samples (10 mL/visit) at V1 and at each additional visit (A1, A2, A3). Subjects consenting to the sub-study of cell-mediated immunity will be required to provide an additional 40mL at each of these timepoints (V1, A1, A2,A3).
Rationale: Changes made to reflect sample requirements for the main study, the clinical laboratory sub-study and the sub-study of cell-mediated immunity, separately.	
6.2.5 "Biological samples, handling, analysis and storage.	The sentence "A separate information and consent document will be provided" for biobanking has been removed. Potential study subjects will be provided information about biobanking and will be given the opportunity to consent to biobanking within the main study consent form.
Rationale: The clinical sites requested that the optional biobanking information and consent be included in the main consent form to reduce the number of pages to be read by potential study participants,. A lack of consent to biobanking will not preclude participation in the main study.	

Section 6.3.1 Screening	Addition of Urinalysis to the list of test to be done at screening, for consistency with the Appendix 2 Schedule of Events and Section 6.2.2 Screening Laboratory Evaluations.
Rationale: This addition was made to ensure internal consistency within the protocol and to make sure that urinalysis at screening was performed.	
Section 6.3.2 "Vaccination visits"	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 6.3.2 "Vaccination visits"	Clarification provided that inactivated vaccines should not be received 2 weeks prior to 2 weeks after any study vaccination and attenuated vaccines should not be received 4 weeks prior to 4 weeks after any study vaccination.
Rationale: Sentence restructured to improve clarity.	
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 and removal of the 7-day laboratory evaluation in the full study cohort. Follow up telephone call is now done 7 days after each vaccination.	
Section 6.3.6 "Sub-study additional visits"	Additional study visits required for subjects enrolled at select sites for the clinical laboratory sub-study and optional cell-mediated sub-study are defined.
Rationale: To clarify the additional visit requirements at select sites for the clinical laboratory and cell-mediated immunity sub-studies.	
Section 6.3.7 "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 following vaccination.	
Multiple sections	Correction made from [1 mL, 10 µg HBsAg, $Al(OH)_3$ 0.5 mg/mL without thimerosal] to [1 mL, 10 µg HBsAg, **Aluminum** 0.5 mg/mL without thimerosal]
Rationale: Distinction provided regarding the adjuvant, aluminum hydroxide, and the amount of aluminum alone (0.5mg/mL) in the investigational product, Sci-B-Vac™.	

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. The 1 mL dose of Engerix-B® containing 20 µg of HBsAg is the form 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 adolescents 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%[18]. 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

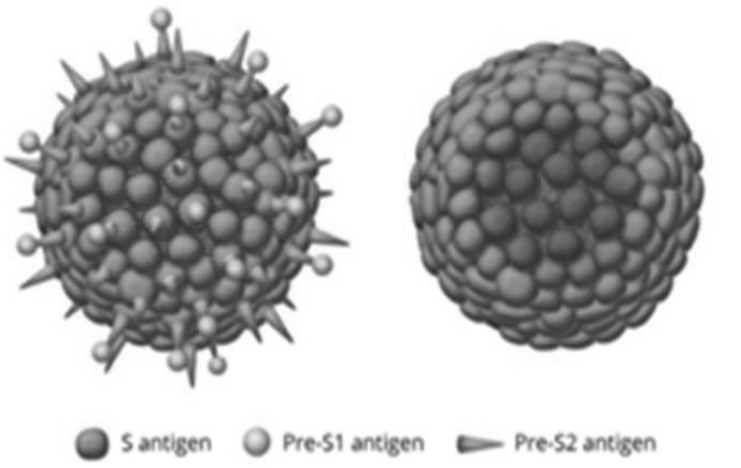
incremental approach consisting of: 1) giving one additional vaccine dose followed by anti-HBs testing 1–2 months later and 2) in the individuals whose anti-HBs levels remains <10 mIU/mL giving two additional vaccine doses, followed by repeat anti-HBs testing 1–2 months later. Similar re-vaccination 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[19]. 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 [20,21]. Pre-S2 may also help in the attachment of HBV to hepatocytes, which may be prevented through an adequate anti-pre-S2 response[22]. 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[23]. 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[24].

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 Study Day 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 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 Co-primary objectives

- 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 the three-dose regimen of Engerix-B® in adults ≥18 years old i.e. the lower bound of the 95% two-sided confidence

interval (CI) of the difference between the SPR in the Sci-B-Vac™ arm minus the SPR in the Engerix-B® arm, achieved 4 weeks after receiving the third vaccination, will be > - 5%.

And

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

2.2 Secondary objectives

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

2.3 Exploratory Objectives

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

subjects recruited to an optional sub study at select sites (~n=50-75 subjects/treatment arm).

3 STUDY DESIGN AND ENDPOINTS

3.1 Study design

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

Randomization will be stratified by study center and age (18-44 years, 45-64 years and ≥ 65 years). There will be targeted enrollment to the ≥45 year old age groups (80% of study population) to ensure adequate power to also establish superiority of Sci-B-Vac™ in older adults (≥45 years old), a co-primary outcome, according to the parameters detailed is Section 9.5.1. There will also be equal representation (i.e. 40%) of study subjects in the two older age strata (45-64 years and ≥ 65 years) to ensure good representation across the spectrum of older adults.

The study subjects, the study center staff performing outcome measurement, and the sponsor will be blinded to vaccine allocation. Study vaccines will be prepared by a qualified unblinded study center staff. 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. After visual inspection, the vaccine will be covered and immediately administered. The unblinded health personnel will not communicate what vaccine was administered to the subject or study centre staff performing the outcome measurements.

Upon confirmation of enrollment, all subjects will be asked to come for a total of 6 visits (denoted V1, V2, V3, V4, V5, and end of study visit, V6). Subjects will be followed a minimum of 48 weeks after receiving the first vaccination on Study Day 0, with at least a 24-week follow-up safety assessments after receiving the third injection.

Each subject will receive one injection of 1 mL of Sci-B-Vac™ or Engerix-B® in the deltoid muscle at 0, 4 weeks (Study Day 28), and 24 weeks (Study Day 168), as per the current recommended HBV immunization schedule in adults.

There will be a safety follow-up telephone call 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.

Immunogenicity (measurement of anti-HBs, pre S1 and pre S2 antibody levels and characteristics) will be assessed at baseline and on Study Days 28, 56, 168, 196, and 336. Immunogenicity will be evaluated using a validated quantitative antibody test against HBsAg. Anti pre-S1 and anti pre-S2 investigations will be exploratory.

Safety evaluations will include standardized methods for local and systemic vaccine reactions, repeated vital signs and physical examinations, 48-week follow-up for SAE, medically significant events or new onset of chronic illness (at least 24 weeks after receiving 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 2 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. From among the subjects participating in the clinical laboratory sub-study, ~50-75 subjects/treatment arm will be invited to enroll in a optional study on cell-mediated immunity. A separate consent form will be provided for the sub-study on cell mediated immunity. Subjects consenting to participate will be required to provide additional blood samples, on Study Days 0, and Study Days, 7, 28, 56, beyond those being collected for the clinical laboratory sub-study.

3.2 Primary endpoint

- Seroprotection rate 4 weeks after receiving third vaccination with either Sci-B-Vac™ or Engerix-B®, on Study Day 196. Seroprotection is defined as anti-HBs levels ≥ 10 mIU/mL in serum. Seroprotection rate is the percentage (%) of subjects achieving seroprotection. A validated quantitative antibody test will be used to measure anti-HBs levels in serum.

3.3 Secondary endpoints

- SPR on Study Days, 56 and 168, 4 weeks and 20 weeks after receiving the second Sci-B-Vac™ vaccination (just prior to receiving the third vaccination), and the SPR on Study Day 196, 4 weeks after receiving the third Engerix-B® vaccination
- Number (%) of subjects-reported, solicited (on the day of vaccination and during the next 6 days), unsolicited AE (on the day of vaccination and during the next 27 days), and number of Serious SAEs, medically significant events (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, and/or physical examination findings compared to baseline.

3.4 Exploratory endpoints

- Geometric Mean Concentration (GMC) of anti-HBs in serum, in both study arms, at baseline and on Study Days 28, 56, and 196, 4 weeks after each vaccination with either Sci-B-Vac™ or Engerix-B®, and on Study Day 168 and 336.
- SPR in both study arms at baseline and on Study Days 28, 56 and 168 and on Study Day 336.
- Proportion of subjects achieving anti-HBs levels ≥ 100 mIU/mL in serum, in both study arms, on Study Days 28, 56, and 196, 4 weeks after each vaccination with either Sci-B-Vac™ or Engerix-B®, and on Study Day 168 and 336.

- Rate of non-response (defined as the proportion of subjects not attaining anti-HBs levels≥ 10 mIU/mL), on Study Day 196, 4 weeks after receiving the third vaccination with either Sci-B-Vac™ or Engerix-B®.
- The GMC of anti pre-S1 antibody and anti pre-S2 antibody in serum, in both study arms, at baseline and on Study Days 28, 56, and 196, 4 weeks after each vaccination with Sci-B-Vac™ or Engerix-B® and on Study Day 168 and 336.
- 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)
- Cell-mediated immunity against HBs at baseline (Study Day 0) and on Study Days 7, 35 and 175 with either Sci-B-Vac™ or Engerix-B® (optional sub study in a subset of subjects participating in the clinical laboratory sub-study).

4 STUDY ENROLLMENT AND WITHDRAWAL

4.1 Subjects population

The study will enroll approximately 1,564 subjects, age ≥ 18 years old, in ~ 30 study centers in Europe, Canada, and the U.S. Individuals of any gender, race and ethnic groups are eligible for this trial.

In order to ensure that subjects in the older age group are adequately represented, since this age group may benefit the most from Sci-B-Vac™, common chronic conditions in aging populations such as, for instance, type 2 diabetes, high blood pressure, COPD, chronic arthritis, or asthma will be accepted if the condition is adequately controlled, as determined by the investigator.

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 years.
3. In stable health as determined by a physical examination and laboratory tests values. Common chronic conditions such as, but not limited to, type 2 diabetes, high blood pressure, COPD, asthma will be accepted if the condition is well controlled, as determined by the investigator, **and** not meeting the exclusion criteria. For subjects > 65 years old, Frailty Index ≤3 [17](see Appendix 1).
4. If female:

   either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy),

   OR

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 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 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 a prednisolone-equivalent dose > 20 mg /day (Inhaled and topical steroids are allowed.
3. Known history of immunological function impairment, including but not limited to:
   a) autoimmune diseases (e.g., multiple sclerosis, type 1 diabetes, myasthenia gravis, Crohn disease and other inflammatory bowel diseases, celiac disease, systemic lupus erythematosus, scleroderma, including diffuse systemic form and CREST syndrome, systemic sclerosis, dermatomyositis polymyositis, rheumatoid arthritis, juvenile idiopathic arthritis, autoimmune thyroiditis -including Hashimoto thyroiditis, Grave's or Basedow's disease, immune thrombocytopenic purpura, autoimmune hemolytic anemia, autoimmune hepatitis, psoriasis, vitiligo, vasculitis, Guillain-Barré syndrome, Addison's disease, Bell's palsy and alopecia areata);

   OR

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

   OR

   c) primary immunodeficiency disorders (e.g. common variable immune deficiency (CVID), Defective phagocytic cell function and neutropenia syndromes, complement deficiency).
4. Pregnancy or breastfeeding.
5. Immunization with attenuated vaccines (e.g. MMR) within 4 weeks prior to enrollment.
6. Immunization with inactivated vaccines (e.g. influenza) within 2 week prior to enrollment.
7. Has received blood products or immunoglobulin within 90 days of enrollment 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 colony 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 a 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 (Engerix-B® or Sci-B-Vac™).
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 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) $\leq$60 mL/min/1.73 m^2 at screening.
19. Uncontrolled diabetes mellitus (defined as HbA1C >8.5%).
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. Any laboratory test abnormality that would be considered of Grade 1 severity or above as per Appendix 4 **and** is considered as clinically significant by the investigator. Grade 3 severity or above is exclusionary, regardless of clinical assessment.
22. Diagnosis of advanced stage heart failure (New York Heart Association (NYHA) class III or IV – see Appendix 5) or Unstable Angina

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 the conduct of any study-related activity. Consenting subjects will be informed that the study site staff will provide them with their serology results at the end of the study, after the database has been locked. Eligible subjects will also be asked to provide their consent to have their blood samples de-identified and securely stored and used for future research (bio banking) by the sponsor after the study is completed and the blood samples are no longer required for validation studies. De-identification is the process by which a coded sample is relabeled with a unique second code, as an added step to preserve confidentiality, with limited and restricted access to the list linking the codes. Lack of consent to the bio banking of blood samples will not preclude participation in the main study.

At select study sites, study subjects will also participate in a clinical laboratory sub-study. All subjects enrolled at these select sites will be asked to come for three additional visits (A1, A2, A3) and to provide four additional blood samples, beyond those required for the main study. Blood samples for the clinical laboratory sub-study will be collected at V1 (Study Day 0) and one week after each vaccination, at A1 (Study Day 7), A2 (Study Day 35) and A3 (Study Day 175). A small subset of subjects participating in the laboratory sub-study will be invited to participate in an optional sub-study on cell-mediated immunity. Subjects consenting to the cell-mediated sub-study will be required to provide an additional blood sample at V1 (study Day 0) and at each of the additional visits (A1, A2, A3). Lack of consent to the optional sub-study on cell mediated immunity will not preclude participation in the main study or the clinical laboratory sub-study. .

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 a member of the study center staff will complete the protocol-specific eligibility checklist in the interactive web response system (IWRS). Access to the IWRS randomization page will be through individual login and password.

The authorized staff will be prompted to complete the enrolment page in the IWRS including the subject's age 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 two study arms. A confirmation of the randomization (blinded) and the study ID 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 notification, which must be filed in a locked area/computer folder not accessed by the blinded 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 assess, record, and report AEs and SAEs as instructed in Section 7 (ASSESSMENT OF SAFETY).

Withdrawals for any reasons 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 concluding visit (V6) /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 inquire about changes 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 recorded in the electronic case report form (eCRF). The investigator will document whether the decision to withdraw a subject from the study 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
- 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 treatment, 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 End of Study Visit (V6) 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 if there is sufficient reasonable cause. 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, the relevant ethical bodies, and all regulatory authorities.

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

Study agents ordering, shipping, receiving, storage and handling is detailed in the pharmacy manual.

5.1 Sci-B-Vac™

5.1.1 Acquisition

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

5.1.2 Formulation and labelling

Sci-B-Vac™ will be supplied 1 mL single-dose vials.

Each 1.0 mL single-dose vial contains 10 µg of hepatitis B surface antigens adsorbed on 0.5 mg aluminum as aluminum hydroxide , sodium chloride, potassium chloride, disodium hydrogen phosphate dodecahydrate, potassium dihydrogen phosphate anhydrous and water for injection.

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.
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

This is a double-blind study. 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 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 unblinded qualified health personnel, whose sole role is to prepare and administer the allocated study vaccine and to perform activities requiring 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 needle length used for the vaccine administration must be adjusted to the subjects BMI to ensure intramuscular administration and to avoid subcutaneous vaccine leakage. The unblinded health personnel will have no other role in the study and 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.

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). 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, if possible, and placed 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. 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.

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 post vaccination. The observation period will include an assessment for rare adverse 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).

Subjects will be contacted by study center staff over the telephone 7 days (+/- 2 days) after each vaccination visit to inquire about local or systemic adverse reactions and may be asked to come to the clinic for a clinical assessment, if warranted. 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 6.1.10 and 7 for further details on the recording, assessment, and reporting of AE 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 not to be seroprotected (anti-HBs levels < 10mIU/mL in serum) after completing the three-dose regimen of the study vaccine 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 conducting any study-related activity.

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, race, ethnicity, height, weight, 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 and GFR.

The age at randomization will be required to randomize the subjects according to their age at enrollment (i.e., 18-44 years , 45-64 years or ≥ 65 years).

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 vaccination temporarily precludes injection, the visit will be rescheduled within the allowed interval for the visit. 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 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 interval for the visit.

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, which must be filled in a locked area/computer folder not accessible by blinded study center staff.

6.1.8 Study product administration

After completing all prerequisite procedures prior to vaccination, 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. The 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 this 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 a vaccine, must be checked and recorded in the eCRF.

The use of the following concomitant medications/products/vaccines 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 following concomitant medications/products/vaccines 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
- 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 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], 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 daily the maximum pain, tenderness and pruritus [itchiness] 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 body temperature (oral) and any local/systemic AEs (i.e., on the day of vaccination and during the next 6 days) or any solicited or unsolicited AEs (i.e., on the day of vaccination and during the next 27 days occurring after injection) on the 28-day diary card. The study center will contact the subject 7 days (+/-2 days) after each vaccination to assess subject status and to remind the subject to complete the diary cards and return them 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.
  - 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 Study Day 336.
  - Instructed to bring their diary cards to clinic visit on Study Days 28, 56, and 196 as follows: the diary card provided on Study Day 0 will be collected on Study Day 28; the diary card provided on day 28 will be collected on Study Day 56, and the diary card provided on 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 HBV vaccine.

- Be informed of the appointments (date and time) for the next planned visits to the study center (Study Days 28, 56, 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 from the diary card transcribed to English from another language 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 vaccines 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 weight in the eCRF using the CKD-EPI Creatinine Equation (2009)[25]
    - GFR≤ 60 mL/min/1.73 m^2 is exclusionary

- Alkaline phosphatase (AP), alanine transaminase (ALT: SGPT), aspartate transaminase (AST: SGOT), total and conjugated bilirubin, gamma-glutamyl-transferase (GGT)
- HbA1C will be tested in subjects with a known type 2 diabetes if a previous HbA1C test result is unavailable and/or is > 3 months old, in order to verify that diabetes is controlled. HbA1C >8.5 % is exclusionary.

- 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 4 will be interpreted within the subject's specific context (subject's medical history, physical examination, other laboratory tests) by the investigator to determine whether the subject still meets 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 anti-HBs, anti pre-S1 and anti pre-S2 levels and characteristics) will be assessed at baseline (V1), on Study Days 28 (V2), 56 (V3), 168(V4), 196 (V5), and on Study Day 336 (End of Study Visit – V6) in all subjects.

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

The assay to measure anti pre-S1 antibody and anti pre-S2 antibody is currently under development and will be validated prior to its use in the phase 3 trial.

In study subjects that have agreed for their unused blood samples to be used for future research by the study sponsor (bio banking), de-identified frozen serum aliquots will be stored in a secure biorepository held by the study sponsor for future use. De-identification is the process by which a coded sample is relabeled with a unique second code, as an added step to preserve confidentiality, with limited and restricted access to the list linking the codes. No genetic testing will be performed.

6.2.4 Sub-Studies

6.2.4.1 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 (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 2 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))

6.2.4.2 Optional sub study of cell-mediated immunity directed against HBs

Cell-mediated immunity directed against HBs and related mechanistic studies will also be studied on a small subset of subjects (~50-75 subjects/treatment arm), recruited from among the subjects participating in the clinical laboratory sub-study (see 6.2.4.1 above). Participation in the sub-study of cell-mediated immunity is optional, and will require a separate consent.

Subjects who agree to participate in the sub-study of cell-mediated immunity will be asked to provide 4 additional blood samples, beyond those required for the clinical laboratory sub-study, at V1 (Study Day 0) prior to vaccination and at each of three additional visits (A1, A2, A3) 1 week after each vaccination with either Sci-B-Vac™ or Engerix-B® (Study Days 7, 35, 175).

Lack of participation in the optional sub-study of cell-mediated immunity will not preclude participation the clinical laboratory sub-study or the main study.

6.2.5 Biological samples handling, analysis and storage

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. For the clinical laboratory sub-study participants who also consent to participate in the optional sub-study of cell-mediated immunity, an additional 40 mL 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 until the Sci-B-Vac™ has been approved, for confirmation purposes only, for a maximum of 60 months (5 years) after the study has been completed. No genetic testing will be performed.

Study subjects will be offered the possibility to donate any unused stored blood samples for use in future research projects in HBV testing and vaccine development. De-identified bio banked frozen serum aliquots from consenting study subjects will be stored in a secure biorepository held by the study sponsor for future research. No genetic testing will be performed.

If the study subject does not agree to donate unused stored blood samples, they will not be used in other research projects and they will be destroyed once the vaccine is approved in Canada, the U.S. and Europe or after a maximum period of 5 years after the end of the study, whichever comes first.

Detailed information on biological sample handling and analysis is provided in the laboratory manual.

6.3 Study schedule of events

A schedule of events is available in Appendix 2.

6.3.1 Screening

The screening will be conducted within 28 days (4 weeks) of Visit 1. 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 Visit 1 prior to injection)
- Height and weight
- Concomitant medications
- Urine Pregnancy test (in females of childbearing potential)
- Blood sampling for screening hematology, blood chemistry and serology tests (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.

6.3.2 Vaccination visits

Vaccination will be done at Visit 1, 2 and 4 (Study Day 0, Study day 28 (-3 days/+7 days), and Study day 168 (+/- 7 days, respectively).

On Day 0 (Visit 1), 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 (Study Day 28) and there will be a review of any local and systemic reactions. There will also be a blood sample collection prior to each vaccine administration.

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

At each vaccination visit the following will be done:

- Concomitant medications will be recorded, including other vaccines.

- 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 for Immunogenicity tests (measurement of anti-HBs, anti pre-S1 and anti pre-S2 levels and characteristics), on Study Day 0, Study Day 28 and Study Day 168 will be taken, prior to vaccination.
- Blood samples for assessment of clinical laboratory parameters will be taken on Study Day 0, prior to vaccination (select sites).
- Vital signs will be assessed before and after the injection of study vaccine. Any abnormal vital sign after injection should be reassessed.
- Physical/History-directed physical examination will be done.
- Eligibility for receiving treatment will be reviewed by the investigator.
- Study vaccine will be administered.
- Subject will be monitored for 30 minutes after the injection.
- A diary card will be provided at each vaccination visit. In addition, at Visit 2 (Study Day 28), the diary card provided at Visit 1 will be collected and reviewed. Adverse events will be recorded in the eCRF.
- 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 or 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), or for 4 weeks after V2 or within 4 weeks of the third vaccination on V4 (Study Day 168).

6.3.3 Safety follow-up

The study center will contact the subject by telephone 7 days (+/- 2 days) after each vaccination to assess subject's status and to remind the subject to complete the diary cards and return them at their next study visit. 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 a supplemental visit for clinical assessment of an adverse event if warranted, as determined by the investigator. The supplemental visit will be recorded in the eCRF.

6.3.5 Immunogenicity visits

Additional immunogenicity visits will be scheduled on V3 Study Day 56 (-3/+7 days) and V5 Study Day 196 (+/-7 days). At these clinical visits, the following will also be done:

- Physical/History-directed physical examination.

- Blood samples for measurement of anti-HBs, anti pre-S1 and anti pre-S2 levels and characteristics will be taken on Study Day 56 and Study Day 196.
- V3 should be scheduled at least 3 weeks after V2
- Diary card provided at the previous vaccination visit will be reviewed.
- Adverse events and the use of concomitant medications will be recorded in the eCRF.
- The next visit will be scheduled.
- At V3 (on day 56) subjects will be reminded that they should not receive inactivated vaccines 2 weeks prior or attenuated vaccines 4 weeks prior to the next vaccination at V4 (on Study Day 168).
- V5 should be scheduled at least 3 weeks after V4

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 2 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®.

Subjects recruited from the clinical laboratory sub-study to participate in the optional sub-study of the cell-mediated immune response, will be asked to provide an additional blood sample on Study Day 0 (Visit 1) and at A1, A2 and A3 on Study Day 7 (- 3/+7 days) and Study Day 35 (-3/+7 days) and Study Day 175 (-3/+7 days) to investigate and compare cell-mediated immune response following vaccination with either Sci-B-Vac™ or Engerix-B®.

6.3.7 End of study visit

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

- Physical/History-directed physical examination.
- Blood samples for measurement of anti-HBs, anti pre-S1, and anti pre-S2 levels and characteristics will be taken.
- SAE, 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 lack of seroprotection (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;
- Preexisting symptoms or conditions which worsen during a study.

7.1.2 Serious Adverse Events

A Serious Adverse Event (SAE):

- 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 another medically important 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 adverse event may jeopardize the subject or may require intervention to prevent more serious outcomes, then the adverse event should be treated as serious.

7.1.3 Preexisting conditions

In this trial, a preexisting condition (i.e., a disorder present before the adverse event reporting period started) should not be reported as an adverse event unless the condition worsens during the adverse event 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 noninvasive and invasive procedures, such as surgery, should not be reported as 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 adverse event reporting period should be reported as an adverse event 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 adverse event 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 3.

7.1.6.3 Laboratory tests abnormalities

Laboratory tests abnormalities 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 4.

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 SAE will also be assessed according to the following categories:

- **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.

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 adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.2 Methods and timing for assessing, and recording safety parameters

Unless specified otherwise all AE occurring between obtaining the subject's written consent to participate in the study 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 received the study treatment 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 for 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 daily on the day of vaccination and for the next 6 days and recorded in the eCRF
- Subjects will be asked to indicate the maximum pain, tenderness and pruritus (itchiness) 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 4) 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 SAE, expected or unexpected, medically significant event or new onset of chronic illness occurring between obtaining the subject's written consent to participate in the study and the last study visit will be documented in the eCRF, first in an AE form. For SAE, upon completion of the AE form, and confirmation that the AE is an SAE, the investigator or delegates 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 not post-menopausal or surgically sterile 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 SAE 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 will appoint a Medical Monitor/pharmacovigilance agent who will report adverse events to the appropriate regulatory authorities as outlined below.

The study sponsor or delegates 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 delegates must submit it as soon as possible, but no later than 15 calendar days after receiving the request.

The study sponsor or delegates 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

Unblinding procedure (which incorporates ICH E2A guidance, EU Regulations on clinical trials on medicinal products for human use and US Federal Regulations) is to unblind the report of any SAE that is unexpected and attributable/suspected to be attributable to the investigational product/product, prior to regulatory reporting. Causality will be determined by the investigator.

The IRB/REB will receive blinded or unblinded safety reports in keeping with local requirements. Suspected unexpected serious adverse reactions (SUSAR) reports will be distributed to the investigator and IRB/REB in compliance with local regulations.

The Medical Monitor will be responsible for the unblinding of events that meet the study stopping rules, if this is determined to be necessary for evaluation purposes by the data monitoring committee.

The blind should ordinarily be broken for regulatory submission.

Unblinding in case of an emergency is described below. However, it should be noted that is not anticipated that such occurrence will be encountered in the conduct of the study since it is unlikely that the knowledge of the vaccine 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, the

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 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)
- 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
- 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 3)

**FDA Grading of Clinical Laboratory Abnormalities (Appendix 4)

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.

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 in 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, including monitoring by designated unblinded personnel, 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 study center 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 by the monitor according to the CMP

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

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

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

Targeted enrollment by age strata will be as follows:

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

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

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

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

9.2 Randomization

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

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

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 Intent-to-Treat (ITT)

All subjects in the All Enrolled Set who were randomized.

9.3.4 Full Analysis Set (FAS)

All subjects in the All Enrolled Set who receive at least one vaccination and provide at least one evaluable serum 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.

9.3.5 Per Protocol Set (PPS)

All subjects in the FAS who:

- received all 3 vaccinations
- have an evaluable serum sample at the time point of interest
- are sero-negative 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 [as per exclusion criteria], if the medication and the timing of its administration is considered to have a significant impact on the reliability of subject immunogenicity result
- subjects with a deviation identified through monitoring visits or otherwise, where the deviation is judged to impact the reliability of subject immunogenicity result

9.3.6 Sub Study Analysis Set (SSA)

All subjects in the All Enrolled Set who actually receive at least one dose of study vaccination, participated in the sub-study, and provide data at baseline and at least one post baseline visit for cell mediated immunity.

9.3.7 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)
- Age cohort (18-44 years, 45-64 years, ≥65 years)
- Diabetes (Diabetic vs non-diabetic)
- Daily alcohol consumption (≥ 4 drinks/day vs 2-3 drinks/day vs 0-1 drink/day)
- Non–study licensed vaccines (no vaccination vs vaccination)
- 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.

9.5 Co-Primary Objectives

9.5.1 Co-Primary Hypotheses

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

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

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

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

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

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

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

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

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

lower bound is greater than 5%, Sci-B-Vac™ will be declared clinically superior to Engerix-B®, and the study will be considered a success.

9.5.2 Statistical Methods for Co-Primary Analyses

For the primary endpoint of SPR at day 196, 4 weeks following the third vaccination, data from all centers will be pooled for the primary analysis. The difference in adjusted proportions and two-sided 95% Cis, calculated using the Miettnen and Nurminen method, will be reported. 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 analysis will comprise a complete case analysis only without introducing any bias. Imputation methods will not be used. The co-primary non-inferiority analysis will use the PPS. For the co-primary superiority analysis, only subjects in the FAS who are sero-negative will be used.

The impact of center will be investigated through funnel plots.

Sensitivity analyses using the same modeling approach outlined above will also be conducted using the FAS, for the non-inferiority co-primary analysis. These analyses will be reported both with and without patients in the FAS who are seropositive at baseline. Sensitivity analyses using the ITT analysis set will be conducted for the superiority co-primary analysis. For these ITT analyses, patients with missing data at day 196 (4 weeks following the third vaccination) will be included and treated as failures. These analyses will be reported both with and without patients who are seropositive at baseline. Additonal sensitivity analyses will be conducted using a Log Linear model, to adjust for age group. Factors for treatment and age group will be included in the model.

Analyses of the co-primary endpoints will also be conducted and reported by key sub-groups using the sub-groups identified in Section 9.3.7.

9.6 Secondary Immunogenicity Objectives

9.6.1 Secondary Immunogenicity Hypotheses

If the co-primary hypotheses are significant, the following secondary hypotheses will be tested in the following pre-specified order, with each hypothesis using a two-sided 5% significance level.

1) Non-Inferiority of Sci-B-Vac™, 20 weeks following the second vaccination, compared to Engerix-B®, 4 weeks following the third vaccination, will be assessed using the PPS3 analysis set for the entire study population (i.e., adults ≥ 18 years old). The non-inferiority margin is set at 5%. The null and alternative hypotheses are as follows;

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

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

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

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

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

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

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

9.6.2 Statistical Methods for Secondary Immunogenicity Analyses

The secondary endpoints of SPR 4 weeks following the second vaccination with Sci-B-Vac™ and 20 weeks following the second vaccination Sci-B-Vac™, each compared with SPR 4 weeks following the third vaccination with Engerix-B® will be analyzed using data from all centers will be pooled together. The difference in adjusted proportions and two-sided 95% Cis, calculated using the Miettnen and Nurminen method, will be reported. will be calculated based on these models. For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the analysis will comprise a complete case analysis only without introducing any bias. Imputation methods will not be used. These analyses will be conducted using the PPS.

The impact of center will be investigated through funnel plots.

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

Analyses of the above secondary endpoints will also be conducted and reported by key sub-groups using the sub-groups identified in Section 9.3.7.

9.7 Exploratory Immunogenicity Endpoints

Analysis of all exploratory immunogenicity endpoints will be based on the PPS, unless otherwise indicated.

Geometric Mean Concentration (GMC)

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 at day 28, day 56, day 168, day 196 and day 336 will each be determined using an analysis of covariance (ANCOVA) model with factors for treatment, age group, and a covariate for the log transformed pre-vaccination (baseline) titer. Antibody GMCs, associated standard errors, two-sided 95% CIs and median, minimum, and maximum titer values will be determined and presented by treatment group. The median, minimum, and maximum values will be reported on the actual titer values, rather than the log scale. The difference in GMCs between the two treatment groups, and associated two-sided 95% CIs will also be presented. For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, this analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

The above analyses will be conducted and reported for all subjects age ≥ 18 years old and for subjects age ≥ 45 years old. Analyses of GMC in both age cohorts will also be reported by sub-group using the sub-groups identified in section 9.3.7. Sub-group analyses will include additional factors in the model, a factor for the sub-group of interest and the interaction between the sub-group and treatment.

Binary Data

All binary data will be summarized using frequency counts and percentages, by time point. Data from all centers will be pooled for these analyses. The difference in adjusted proportions and two-sided 95% CIs, calculated using the Miettnen and Nurminen method, will be reported. Additonal sensitivity analyses will be conducted using a Log Linear model, to adjust for age group. Factors for treatment and age group will be included in the model. For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the analysis will comprise a complete case analysis only without introducing any bias. Imputation methods will not be used.

The above analyses will be conducted and reported for all patients age ≥ 18 years old and for patients age ≥ 45 years old. Analyses of binary data in both age cohorts will also be reported by sub-group using the sub-groups identified in section 9.3.7.

Sub Study

Cell mediated immunity data collected in the sub-study will be summarized for the Sub Study Analysis Set using descriptive statistics.

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. All safety analyses will be presented by severity for each age group and for each treatment group 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 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 3. 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).

9.8.3 Analysis of Spontaneously Reported Adverse Events

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 by interval of study observation. 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

9.8.4 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. Data will be reported by treatment group. 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 3 for vital signs and Appendix 4 for laboratory parameters).

9.9 Interim Analysis

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 PI. 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 vaccine reaction 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 center, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations; otherwise, the minimum retention period will default to 25 years.

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

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 Quality Assurance and Quality Control, Section 5.1.15.20 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 local IRB according to institution policies. The site PI/study center staff is responsible for knowing and adhering to their institution policies.

11 QUALITY CONTROL AND QUALITY MANAGEMENT

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.

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 ClinicalTrial.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 also 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 (IEC) 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 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 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 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 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 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 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: CHSA* FRAILTY SCALE[17]

Table 2: CHSA Frailty Scale

Index	Description
1	Very fit — robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
2	Well — without active disease, but less fit than people in category 1
3	Well, with treated comorbid disease — disease symptoms are well controlled compared with those in category 4
4	Apparently vulnerable — although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms
5	Mildly frail — with limited dependence on others for instrumental activities of daily living
6	Moderately frail — help is needed with both instrumental and non-instrumental activities of daily living
7	Severely frail — completely dependent on others for the activities of daily living, or terminally ill

*: CSHA = Canadian Study of Health and Aging.

15.2 Appendix 2: Schedule of Events

Table 3: Schedule of Events (main study and sub-studies)

	Screening	V1	Phone Safety Follow-up	V2	Phone Safety Follow-up	V3 (i)	V4	Phone Safety Follow-up	V5 (j)	V6 End of Study Visit
Timelines (days)	-28	0		28		56	168		196	336(a)
Range (days)	-28 to 0		V1 + 5-9	-3/+7	V2 + 5-9	-3/+7	+/-7	V4 + 5-9	+/-7	+/-14
Screening										
Informed Consent	X									
Inclusion & Exclusion Criteria	X									
Physical Examination (b)	X	X		X		X	X		X	X
Medical History	X									
Height and weight	X									
Medications	X									
HBV serology	X									
HIV and HCV serology	X									
Urine Pregnancy test	X	X		X			X			
Blood tests: CBC, liver and renal function, HbA1C if indicated	X									
Urinalysis	X									
Randomization		X								
Vaccination		X		X			X			
Immunogenicity										
Anti-HBs		X(c)		X(c)		X	X(c)		X	X
Anti pre-S1, anti pre-S2		X(c)		X(c)		X	X(c)		X	X
Safety Assessments										
Vital signs	X	X(d)		X(d)			X(d)			
Subject instructed to complete diary		X	X	X	X		X	X		

Recording Local & Systemic Reactions		X	X(e)	X	X(e)		X	X(e)		
Recording Concomitant Medications	X	X	X	X	X	x	X	X	X	X
Unsolicited AEs	X	X	X(g)	X(g)	X(g)	X(f)	X(g)	X(g)	X(g)	X(f)
SAEs, medically significant event, NOCI (h)	Continuous									
Sub-Studies (only at select sites)			A1*		A2*			A3*		
Serum chemistry , Hematology		X(c)	x(k)		x(k)			x(k)		
Cell-mediated immunity		X(c)	x(k)		x(k)			x(k)		

(a) Or earlier in case of withdrawal
(b) Full physicals to be done at screening or pre-vaccination at Day 0. History-directed physicals can be completed at subsequent visits.
(c) Blood sample at V1, V2 & V4 will be taken before vaccination
(d) Vital signs will be recorded before and 30 minutes after each vaccination.
(e) Subjects will be instructed to record solicited and unsolicited AES. There will be a telephone call 1 week after each vaccination to inquire about reaction to vaccine. If there is a reaction the subject may be asked to come for a supplemental visit (not represented in this table) to assess severity at the discretion of the investigator. Follow-up until resolution.
(f) Only AEs requiring medical attention
(g) All AEs
(h) NOCI: new onset of chronic illness
(i) V3 should be scheduled at least 3 weeks after V2
(j) V5 should be scheduled at least 3 weeks after V4
(k) Blood sample collected 7 days (-3/+7 days) after vaccination

* Additional visits (A1, A2 and A3) required for study subjects **at select sites** participating in the clinical laboratory sub-study. A small subset of subjects participating in the clinical laboratory sub-study will be eligible to participate in an optional sub-study on cell-mediated immunity.

15.3 Appendix 3: FDA guidelines for grading vaccine reactions

Table 4: FDA Grading of Injection site reactions

	Grade 1	Grade 2	Grade 3	Grade 4
Pain (pain without touching)	Does not interfere with activity	Repeated use of non-narcotic pain reliever	Any use of narcotic pain reliever or prevents daily	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
Pruritis associated with injection See also Skin: Pruritis (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 5: FDA 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	A 39.0 – 40 B 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 6: FDA Grading of 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 > 800gms/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

15.4 Appendix 4: 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 in the laboratory manual.

Table 7: FDA Grading of blood chemistry abnormalities

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
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	--

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
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.

Table 8: FDA Grading of hematology tests abnormalities

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
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	--

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
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.

Table 9: FDA Grading of urinalysis abnormalities

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.

15.5 Appendix 5: NYHA functional classification

Table 10: NYNA Classification of physical activity

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.