CLINICAL STUDY PROTOCOL

AN OPEN LABEL, SINGLE ARM, SINGLE CENTER CLINICAL STUDY IN HEALTHY SUBJECTS TO QUALIFY AN IN-HOUSE REFERENCE STANDARD BATCH OF SCI-B-VAC™

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Protocol Number: SciB018

CRC No. TRC 075/10217

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PROTOCOL SIGNATURE PAGE

Title: An Open Label, Single Arm, Single Center Clinical Study in Healthy Subjects to Qualify an In-House Reference Standard Batch of Sci-B-Vac™

I declare that I have read and understood this study protocol. I agree to abide by this protocol (subject to any amendments agreed in writing between the Sponsor and Principal Investigator). Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of the subjects.

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Date: 4/March 2015

PROTOCOL SYNOPSIS

Study Title	**An Open Label, Single Arm, Single Center Clinical Study in Healthy Subjects to Qualify an In-House Reference Standard Batch of Sci-B-Vac™**
Protocol Number	SciB018
CRC Number	TRC 075/10217
Investigational Product	Sci-B-Vac™
Dosage Form	A single use vial containing 1 ml suspension.
Mode of Administration:	10 µg (in 1 ml) injected intramuscularly into the deltoid muscle. Three Intramuscular injections: on time-0, Month-1 and Month-6
Clinical Phase	IV
Study Objectives	**Primary objective:** To validate the new in-house reference standard vaccine for routine quality control purposes, in compliance with the European Pharmacopeia and the Israeli Ministry of Health. **Secondary objectives:** 1. To characterize the immunological response throughout the study. 2. To monitor the subjects for safety throughout the study period. **Exploratory objectives:** 1. To collect blood samples for the *in vitro* validation of anti-HBs, anti-preS1 and anti-preS2 antibodies assays. 2. To assess the anti-preS1 and anti-preS2 antibodies responses upon vaccination.
Efficacy Endpoints	**Primary endpoint:** Seroprotection rate (SPR), defined as the proportion of subjects with anti-HBs antibody titer at least equal to 10mIU/ml, at Month 7 (i.e one month after the third immunization with Sci–B-Vac™). Subjects early terminated from the study for any reason at any time while having an anti-HBs antibody concentrations ≥ 10mIU/ml will be considered among those who met endpoint. **Secondary endpoints:** 1. SPR at one month after the second injection of Sci-B-Vac™ (i.e. Month 2/visit 4). 2. SPR at month 6 **prior** to the third injection of Sci-B-Vac™ (i.e. Month 6/visit 8). 3. SPR at one month after the first injection of Sci-B-Vac™ (i.e. Month 1/visit 3). 4. The geometric mean concentration (GMC) as determined by anti-HBsAg antibody titers at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.

	Exploratory endpoints: • The anti-preS1 antibody titers measured at Month 0, then at every month until Month 7 inclusive and at months 9 and 12. • The anti-preS2 antibody titers measured at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.
Study Design and Procedures	This is an open label, single arm, single center clinical study in healthy subjects, who were never vaccinated against Hepatitis B and who are HBs antigen, anti-HBc and anti-HBsAg antibodies seronegative. Eligible subjects will be vaccinated 3 times with 10 mcg/ml of Sci-B-Vac™ according to the immunization schedule. The study will consist of three periods: • Screening period: Up to 4 weeks prior to first vaccination • Treatment and follow-up period: 6 months • Post-vaccination follow-up period: 6 months Blood samples will be collected prior to the first vaccination (Month 0), every month until month 7 inclusive, at Month 9 and at Month 12. Safety parameters will be assessed as outlined below and in Section 6.4.
Duration of Study (Clinical Stage)	The duration for an individual subject is approximately 13 months.
Number of Subjects	Up to 84
Inclusion Criteria	1. Healthy males and females between 20 and 40 (inclusive) years of age. 2. Subjects who provide written informed consent to participate in the study. 3. Subjects in general good health in the opinion of the investigator as determined by medical history, vital signs and a physical examination. 4. No clinically significant abnormalities in hematology, blood chemistry, or urinalysis lab tests at screening. 5. Women of child-bearing potential must practice an acceptable method of birth control or practice abstinence during the study period or be surgically sterilized, from screening visit throughout the treatment phase and for 28 days after the last injection and agree to undergo repeated pregnancy tests. 6. Subjects must be able to understand the requirements of the study and must be willing to comply with the requirements of the study.
Exclusion Criteria	1. Known history of significant medical disorder, which in the investigator's judgment contraindicates administration of the vaccine or may interfere with the subject's compliance or the interpretation of study assessment parameters. 2. Any clinically significant abnormality upon physical examination or in the clinical laboratory tests at screening visit. 3. Treatment with immune suppressive agents. 4. Chronic administration (defined as more than 14 days) of

	immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose. 5. History of HBV infection or confirmed exposure to hepatitis B virus. 6. Previous vaccination against Hepatitis B. 7. Positive for HBsAg, anti-HBsAg antibodies, anti-HBc antibodies, anti-HCV antibodies or anti- HIV antibodies. 8. Drug abusers 9. Known hypersensitivity or allergy to any component of the study vaccine. 10. BMI < 18.5 or ≥ 30 Kg/m^2. 11. Known concomitant disease or any other medical condition that is considered by the investigator likely to interfere with the subject's compliance or the interpretation of study assessments. 12. Any acute illness (e.g. acute infection) within 48 hours prior to the first study drug administration that is considered of significance by the Principal Investigator. 13. Female subjects: pregnant, lactating or planning a pregnancy. 14. Any confirmed or suspected immunosuppressive or immunodeficient condition. 15. Receipt of blood or immunoglobulin transfusion six months prior to the first vaccine dose and during the course of the trial. 16. Unwilling or unable (in the judgment of the investigator) to comply with all the requirements of the protocol. 17. Participate in another clinical trial within 3 months prior to first vaccination (calculated from the previous study's last dosing date).
Safety Assessments	The primary safety endpoint is the frequency, severity, and duration of adverse events (AEs), including clinically significant laboratory abnormalities after administration of Sci-B-Vac™. Safety will be evaluated on the basis of the following assessments: • AEs: continuous (starting from informed consent signature until end of study) • Recording of concomitant medications: continuous (starting from informed consent signature until end of study) • Physical examination: on screening and on study termination visit. • 12-lead ECG: on screening and on study termination visit. • Vital signs (sitting BP, HR, RR, oral temperature): on screening, on each treatment (vaccination) visit within 60 minutes before vaccine administration, at 60 (± 15) minutes after vaccination and on study termination visit. • Safety laboratory evaluations (blood and urine): On screening, before each vaccine administration and on study termination visit. Safety laboratory variables are outlined in Appendix B.
Statistical	A total of 84 subjects, are expected to be recruited into study. The trial will follow-up eligible subject for a total duration of 12 months. Two interim

Methodology	analyses are planned to be conducted at the time when approximately 65% subjects and 82.5% of the subjects will reach Month 7 or early terminated the study. **Interim and Final Analyses** Two interim analyses are planned for possible early termination of the study. These analyses will be performed at the time when approximately 65% subjects and 82.5% of the subjects will reach Month 7 or early terminated the study. The first interim analysis will use an alpha level of 0.0109 and the second interim analysis will use an alpha level of 0.0239. The final analysis will use an alpha level of 0.0414 representing the use of the Lan-DeMets correction to type-I error due to multiple testing. **Significance Level** The overall significance level for this study will be 5% using two-tailed tests. **Sample Size Rationale**: Sample size determination was performed under the following assumptions: • The primary endpoint for the study is the Seroprotection Rate (SPR), defined as the proportion of subjects with anti-HBs antibody titer at least equal to 10mIU/ml, at Month 7 (i.e. one month after the third immunization with Sci–B-Vac™). Subjects early terminated from the study for any reason at any time while having an anti-HBs antibody concentrations ≥ 10mIU/ml will be considered among those who met endpoint. • It is expected that the true rate of SPR following treatment with Sci–B-Vac™ is 95% or more. • The principal analysis of the primary endpoint will be a non-inferiority analysis testing the below hypothesis: ✓ H_0: P-p_0 <= -Margin ✓ H_1: P-p_0 > -Margin • Where p_0, the assumed true SPR is 95% and the non-inferiority margin is 12.5%, employing that study will be considered successful if the lower bound of the 95.86% exact CI (using the alpha level at final analysis) will be 82.5% or more (lower non-inferiority limit). • Under these assumptions, sample of 70 subjects will provide a power of 86.1% or more to demonstrate that the observed SPR is non-inferior to the rate of 95%. Sample size is adjusted to a total of 84 subjects to account for an anticipated withdrawal rate of approximately 20%. **Primary Endpoint Definition:** The primary endpoint of the study is the Seroprotection rate (SPR), defined as the proportion of subjects with anti-HBs antibody titer at least equal to 10mIU/ml, at Month 7 (i.e one month after the third immunization with Sci–B-Vac™). Subjects early terminated from the study for any reason at any time while having an anti-HBs antibody concentrations ≥ 10mIU/ml will be considered among those who met endpoint.

	Principal Analysis of the Primary Endpoint: The principal analysis of the primary endpoint will employ a non-inferiority analysis [SAS PROC FREQ with binomial (noninf margin=.125 p=(1-α) exact)] statement will be used for testing the below hypothesis: H_0: P-p_0 <= -Margin H_1: P-p_0 > -Margin Where p_0, the assumed true SPR is 95% and the non-inferiority margin is 12.5%, employing that study will be considered successful if the lower bound of the (1-α) exact CI will be 82.5% or more.

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ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
AE	Adverse Events
ANA	Antinuclear antibodies
ALT	Alanine transaminase
Anti-HBc	Antibodies to hepatitis B core antigen
Anti-HBs	Antibodies to HBsAg
Anti-HCV	Antibodies to hepatitis C virus
AST	Aspartate aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
cm	Centimeter
CRC	Clinical Research Center
CRF	Case Report Form
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMR	Geometric mean ratio
GSK	Glaxo Smith Kline
h	Hours
HBsAg	Hepatitis B Surface Antigen
HIV	Human immunodeficiency virus
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
IMP	Investigational Medicinal Product
IP	Investigational Product
IRB	Institutional Review Board
IRB	Institutional Review Board
Kg	Kilogram
m	Meter
mg	Milligram

Abbreviation/Term	Definition
min	Minute
mITT	Modified intention-to-treat analysis
ml	Milliliter
MOH	Ministry of Health
MSD	Merck Sharp and Dome
N/A	Not Applicable
ºC	Degrees centigrade
OTC	Over the Counter
OTC	Over the counter
PI	Principal Investigator
PQC	Product Quality Complaint
PT	Prothrombin Time
PT/INR	Prothrombin time/International Normalized Ratio (for blood clotting time)
QA	Quality Assurance
R&D	Research and Development
RBC	Red blood cells
RBC	Red blood cell
RDW	RBC distribution width
RR	Respiration rate
SAE	Serious Adverse Event
SOP	Standard Operation Procedures
SPR	Seroprotection rate
SUSAR	Suspected unexpected serious adverse reaction
TASMC	Tel Aviv Sourasky Medical Center
TEAE	Treatment emergent adverse events
WBC	White blood cell
WHO	World Health Organization
µg	Microgram

1 INTRODUCTION

1.1 BACKGROUND – HEPATITIS B VIRUS INFECTION

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus. It can cause chronic liver disease and chronic infection and puts people at high risk of death from cirrhosis of the liver and liver cancer. More than 240 million people have chronic (long-term) liver infections. More than 780 000 people die every year due to the acute or chronic consequences of hepatitis B.

In highly endemic areas, HBV is most commonly spread from mother to child at birth, or from person to person in early childhood. Perinatal or early childhood transmission may also account for more than one third of chronic infections in areas of low endemicity, although in those settings, sexual transmission and the use of contaminated needles are the major routes of infection.

High risk groups include: people who frequently require blood or blood products, dialysis patients, recipients of solid organ transplantations, people interned in prisons, injecting drug users, household and sexual contacts of people with chronic HBV infection, people with multiple sexual partners, as well as health-care workers and others who may be exposed to blood and blood products through their work and travelers who have not completed their hepatitis B vaccination series.

The hepatitis B virus can survive outside the body for at least 7 days. During this time, the virus can still cause infection if it enters the body of a person who is not protected by the vaccine.

Most people do not experience any symptoms during the acute infection phase. However, some people have acute illness with symptoms that last several weeks, including yellowing of the skin and eyes (jaundice), dark urine, extreme fatigue, nausea, vomiting and abdominal pain. In some people, the hepatitis B virus can also cause a chronic liver infection that can later develop into cirrhosis of the liver or liver cancer*.

Five to ten percent of infected adults are unable to eliminate the virus following acute infection, and develop persistent viral infection which lasts more than 6 months; this is designated as a hepatitis B surface antigen (HBsAg) carrier state. It has been estimated that there are >200 million HBsAg carriers worldwide [1].

The first generation, plasma-derived hepatitis B vaccines were developed in the US and France in the late 1970s. In the mid 1980s, second generation recombinant DNA hepatitis B vaccines were constructed in yeasts transfected with HBV-DNA sequences coding for the small HBV envelope protein. These vaccines have gradually replaced the first generation plasma derived vaccines and are currently used for universal vaccination of newborns and adults at risk in >170 countries worldwide. Third generation HBV vaccines containing one or two additional HBV envelope proteins (Pre-S1 and Pre-S2) have been developed in Germany, France and Israel in transfected mammalian cells (Chinese Hamster Ovarian cells). These vaccines have in general an enhanced efficacy as compared to yeast derived vaccines [2,3,4]

1.2 SCI-B-VAC™ PRODUCT DESCRIPTION

Sci-B-Vac™ is a recombinant hepatitis B vaccine, manufactured by SciVac Israel Ltd. It is produced in mammalian Chinese hamster ovary (CHO) cells, transfected with appropriate sequences that code for the HBV envelope proteins SHBs-S, MHBs-pre-S_2, and LHBs-pre-S_1. The gene coding for these antigens, including the native HBs promoter, enhancer, and poly a signal, was

*World health organization, Hepatitis B, Fact sheet N°204 Updated July 2014

cloned into a plasmid vector containing the mouse dihydrofolate reductase (DHFR) expression cassette. The plasmid was used to establish the producer CHO cell line. Transfected cells were selected for $DHFR^+$ phenotype, and gene co-amplification was done with methotrexate. The immunogenicity of the pre-S_2 and pre-S_1 antigens in the final vaccine preparation was demonstrated in BALB/c mice and rabbits, as well as in babies who developed appropriate anti-pre-S1 and anti-pre-S2 antibodies following immunization with Sci-B-Vac™ [5,6,7]. The physical properties of the HBV envelope particles produced in CHO cells and the immune response to HBV nucleocapsid and Pre-S/S envelope proteins have been characterized[5,8-13].

Sci-B-Vac™ is approved by Health Authorities for marketing in 13 countries including Israel, Central Africa, Ivory Coast, Georgia, Gabon, Guinea Equtorial, Hong Kong, Moldova, Niger, Nigeria, Philippines, Senegal and Vietnam.

Since 2005, more than 1.5 million units of Sci-B-Vac™ have been sold in Israel for vaccination against Hepatitis B in babies, children and adults.

1.3 SUMMARY OF CLINICAL STUDIES

To date, thirteen open label clinical studies (plus three extensions) and 4 single blinded clinical studies utilizing Sci-B-Vac™ (also distributed under the trade names Bio-Hep B and Hepimmune) have been completed[16-28].

The clinical development of Sci-B-Vac™ included: two phase I studies in adults [16,17], three phase II dose-range studies in adults [16-18] one in children [19] and four in neonates [20-23], two phase II and one phase III comparative studies in adults [24-26], one Phase II study in children[27] and one Phase II study in neonates[28]. Three of the studies (one in adults and two in children) were extended in order to increase the size of the group vaccinated with Sci-B-Vac™. In the adult phase I studies, subjects received 10 µg of Sci-B-Vac™. Sci-B-Vac™ was given once to prime the immune memory; the first dose was followed by two booster doses at 1 and 6 months after primary immunization[16]. This immunization schedule is set by convention. In the first adult Phase II study in Singapore[16], subjects were randomized to receive 5 µg or 10 µg of Sci-B-Vac™ in three injections. Once tolerability/safety and dose-dependent efficacy were demonstrated, the clinical development of two more adult dose-range studies were performed in Thailand and Israel [17,18,]followed by a dose-range study performed in Poland with children[19] and four neonate studies in Poland, Singapore and Vietnam[20-23]. After seroconversion rates and the efficacy/dose relationship were more firmly established, five comparative studies which assessed the efficacy of Sci-B-Vac™ relative to that of conventional yeast derived vaccines were performed in adults, children and neonates[24-28].

From the early phase II studies it became evident that a significant number of vaccinees develop high anti-HBs titers following vaccination. In study HBN014-01[23], conducted in Vietnam, a dose-response relationship could be demonstrated. More vaccinees who received the 5 µg dose/injection had anti-HBs titers ranging from 1001-10,000 mIU/ml as compared to those who received the 2.5 µg dose/injection. More than 60% of the vaccinees in the 5 µg dose group developed these high titers within three months after the third vaccination. At the end of the study 95.6% (196/205) of the subjects were seroprotected.

The high efficacy of Sci-B-Vac™ was further confirmed in adults[25,26] and in neonates[28]. In these comparative controlled studies conducted in Israel, more than 50% of adult vaccinees who received the 10 µg/dose and neonates who received the 2.5 µg dose had anti-HBs titers above 10,000 mIU/ml after the third vaccination. These percentages were greater than those observed in vaccinees who received the yeast-derived vaccines. Furthermore, no non-responders were observed in

immunized neonates who received 2.5 µg Sci-B-Vac™. In adults, the number of non-responders who received Sci-B-Vac™ was very small (3.5%, 18/513) as compared to vaccinees immunized with Engerix-B® (13.7%, 43/415).

1.4 STUDY RATIONALE

Each Sci-B-Vac™ lot released to the market is tested in comparison to a reference batch, which has to be tested in a human clinical trial.. Therefore, SciVac Ltd. is conducting this study to evaluate the efficacy of a Sci-B-Vac™ batch in support of its qualification as new reference standard. In accordance with the European Pharmacopeia (Ph.Eur. 1056), this reference standard is to elicited at least 95% seroprotection in young, healthy subjects

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To validate the new in-house reference standard vaccine for routine quality control purposes, in compliance with the European Pharmacopeia and the Israeli Ministry of Health

2.2 SECONDARY OBJECTIVES

1. To characterize the immunological response throughout the study.
2. To monitor the subjects for safety throughout the study period

2.3 EXPLORATORY OBJECTIVES

1. To collect blood samples for the *in vitro* validation of anti-HBs, anti-preS1 and anti-preS2 antibodies assays.
2. To assess the anti-preS1 and anti-preS2 antibodies responses upon vaccination.

3 STUDY ENDPOINTS

3.1 PRIMARY ENDPOINT

Seroprotection rate (SPR), defined as the proportion of subjects with anti-HBs antibody titer at least equal to 10mIU/ml, at Month 7 (i.e. one month after the third immunization with Sci-B-Vac™). Subjects early terminated from the study for any reason at any time while having an anti-HBs antibody concentrations ≥ 10mIU/ml will be considered among those who met endpoint.

3.2 SECONDARY ENDPOINTS

1. SPR at one month after the second injection of Sci-B-Vac™ (i.e. Month 2/visit 4).
2. SPR at month 6 prior to the third injection of Sci-B-Vac™ (i.e. Month 6/visit 8).
3. SPR at one month after the first injection of Sci-B-Vac™ (i.e. Month 1/visit 3).
4. The geometric mean concentration (GMC) as determined by anti-HBsAg antibody titers at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.

3.3 EXPLORATORY OBJECTIVES

1. The anti-preS1 antibody titers measured at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.
2. The anti-preS2 antibody titers measured at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.

4 STUDY DESIGN

4.1 OVERALL STUDY DESIGN

This will be a post-marketing, open-label, single arm study in healthy volunteers who had never been vaccinated with any hepatitis B vaccine and who are HBs antigen, anti-HBc and anti-HBsAg antibodies seronegative.

The study assessments will be performed as described in the study flow chart (See Appendix A).

This study will consist of three periods:

Screening Period (Visit 1: up to 1 month prior to first vaccination)

After signing of the informed consent form (ICF), screening procedures will be carried out as specified in Section 6.1.1 and Appendix A.

Treatment and Follow-up Period (Visits 2-8: Months 0-6)

Subject identification number will be assigned to all eligible subjects following assessment of inclusion and exclusion criteria.

All eligible subjects will receive Sci-B-Vac™ vaccine. The treatment phase will include three I.M. doses of Sci-B-Vac™ administered in the deltoid muscle on Month 0, Month 1, and Month 6. Subjects will be followed up for safety evaluations and for efficacy (by anti-HBs, anti-pre-S1 and anti-pre-S2 testing), every month. The previous injection site will be inspected before the second and third administration.

The following assessments will be performed during each treatment visit: recording of AEs and concomitant medications, vital signs and blood tests for quantitative anti-HBs, anti-preS1 and anti-preS2 antibodies and safety assessment (including blood and urine laboratory tests). Female subjects will also undergo a urine pregnancy before each injection . Vital signs are not required on follow-up visits when vaccine is not administered.

Post-Vaccination Follow-up Period (Visits 9-11: Months 7, 9 and 12)

Additional subject follow- up visits will take place 1, 3 and 6 months after the last vaccine administration. On each visit, subjects will be inquired about AEs and concomitant medications, and blood samples for quantitative anti-HBs, anti-preS1 and anti-preS2 antibodies levels will be drawn. The last visit (Month 12) is a study termination visit in which all subjects will also undergo physical examination, laboratory safety assessments (CBC, blood chemistry and urinalysis), vital signs measurement and a 12-lead ECG. In addition, female subjects will undergo a urine pregnancy test.

5 SELECTION OF STUDY POPULATION

5.1 NUMBER OF SUBJECTS

Up to eighty four (84) healthy subjects will be enrolled in the study

5.2 INCLUSION CRITERIA

1. Healthy males and females between 20 and 40 (inclusive) years of age.
2. Subjects who provide written informed consent to participate in the study.
3. Subjects in general good health in the opinion of the investigator as determined by medical history, vital signs and a physical examination.
4. No clinically significant abnormalities in hematology, blood chemistry, or urinalysis lab tests at screening.
5. Women of child-bearing potential must practice an acceptable method of birth control (as specified in Section 8.2) or practice abstinence during the study period or be surgically sterilized, from screening visit throughout the treatment phase and for 28 days after the last injection and agree to undergo repeated pregnancy tests.
6. Subjects must be able to understand the requirements of the study and must be willing to comply with the requirements of the study.

5.3 EXCLUSION CRITERIA

1. Known history of significant medical disorder, which in the investigator's judgment contraindicates administration of the vaccine or may interfere with the subject's compliance or the interpretation of study assessment parameters.
2. Any clinically significant abnormality upon physical examination or in the clinical laboratory tests at screening visit.
3. Treatment with immune suppressive agents.
4. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose.
5. History of HBV infection or confirmed exposure to hepatitis B virus.
6. Previous vaccination against Hepatitis B.
7. Positive for HBsAg, anti-HBsAg antibodies, anti-HBc antibodies, anti-HCV antibodies or anti- HIV antibodies.
8. Drug abusers
9. Known hypersensitivity or allergy to any component of the study vaccine.
10. BMI < 18.5 or ≥ 30 Kg/m^2.
11. Known concomitant disease or any other medical condition that is considered by the investigator likely to interfere with the subject's compliance or the interpretation of study assessments.
12. Any acute illness (e.g. acute infection) within 48 hours prior to the first study drug administration that is considered of significance by the Principal Investigator.
13. Female subjects: pregnant, lactating or planning a pregnancy.

14. Any confirmed or suspected immunosuppressive or immunodeficient condition.
15. Receipt of blood or immunoglobulin transfusion six months prior to the first vaccine dose and during the course of the trial.
16. Unwilling or unable (in the judgment of the investigator) to comply with all the requirements of the protocol.
17. Participate in another clinical trial within 3 months prior to first vaccination (calculated from the previous study's last dosing date).

5.4 SUBJECT IDENTIFICATION

Each subject who signed the informed consent will be identified by a unique CRC internal identification number. Subjects who are dosed will receive an additional subject study ID number.

5.5 SCREENING FAILURES

Subjects who fail to meet the entrance criteria at any stage during the screening period are defined as screen failures. All screen failures will be documented on the screening log, which documents the screening number, subject's initials and reason(s) for screen failure. The screening log will be kept in the Investigators Site File.

Screen failure subjects will be withdrawn from the study and will not count towards the total enrolled or total eligible subjects.

5.6 REMOVAL, REPLACEMENT, OR EARLY WITHDRAWAL OF SUBJECTS FROM TREATMENT OR ASSESSMENT

Subjects are free to discontinue their participation in the study at any time and without prejudice to further treatment. The Investigator must withdraw any subject from the study if that subject requests to be withdrawn, or if it is determined that continuing in the study would result in a significant safety risk to the subject.

Subjects discontinued or withdrawn from the study will **not** be replaced after first dosing.

The subject's participation in this study may be discontinued due to the following reasons:

- Request of regulatory agency, or Sponsor or Principal Investigator
- Subject withdrew consent
- Adverse event (AE)
- Subject is unwilling or unable to continue the study or is lost-to-follow-up
- Subject is non-compliant with study procedures/study protocol
- Investigator decides that withdrawal from the study is in the best interest of the subject
- Subject needs medication not allowed in the protocol
- Any clinically significant change in subject's medical condition.

5.7 HANDLING OF WITHDRAWALS

If a subject is withdrawn from the study or fails to return either at his/her request or at the Investigator's discretion, every effort should be made to determine the reason. This information will

be recorded on the subject's case report form (CRF). All subjects who withdraw from the study prematurely, regardless of cause, should undergo all study termination assessments (see Section 6.1.11). It is vital to obtain follow-up data for any subject withdrawn because of an AE or abnormal laboratory test finding. In any case, every effort must be made to undertake safety follow-up procedures.

If withdrawal is caused by a Suspected Unexpected Serious Adverse Reaction (SUSAR), it will be reported to the institutional review board/independent ethics committee (IRB/IEC) and Sponsor.

5.8 TERMINATION OF STUDY BY SPONSOR

The Sponsor reserves the right to discontinue the study at any time for any reason. Such reasons may be any of, but not limited to, the following:

- Occurrence of AEs unknown to date in respect of their nature, severity, and duration or the unexpected incidence of known AEs
- Medical or ethical reasons affecting the continued performance of the study

Regulatory Authorities also have the right to terminate the study for any reason.

5.9 TERMINATION OF STUDY

A subject will be considered to have completed the study if he or she has completed all assessments at Month 12 of the study.

6 STUDY PROCEDURES AND SCHEDULES

The schedule of activities for this study is shown in Appendix A. No protocol-related procedures should be performed before subjects provide written informed consent. Study related events and activities including specific instructions, procedures, concomitant medications, dispensing of study drugs, and descriptions of AEs should be recorded in the appropriate source documents and CRF.

6.1 VISIT SCHEDULES

6.1.1 Visit 1 - Screening (within 4 weeks before Visit 2)

Subjects will sign an informed consent form and will be assessed for their eligibility to participate in the study.

The following screening assessments will be performed at pre-study for each subject:

- Medical history (including concomitant medications)
- Demographics (gender, date of birth)
- Vital signs: blood pressure and heart rate - supine, respiration rate (RR), oral body temperature
- Height
- Weight
- BMI (calculated as kg/m^2)
- Physical examination

- 12-lead ECG
- Laboratory safety screens as outlined in Appendix B
- For female subjects serum βHCG
- Serology tests as outlined in Appendix A
- Compliance with inclusion/exclusion criteria

The amount of blood drawn in this visit is approximately 31 ml.

6.1.2 Visit 2 - First Vaccine Administration: Month-0 (Day 1)

Dosing day will be designated "**Month 0, Day 1**".

The subjects will be admitted to the CRC in the morning of treatment. They will be interviewed by the CRC study personnel regarding change in concomitant medications or changes to their health status since the Screening visit. Female subjects will undergo a urine pregnancy test, and eligibility of inclusion/exclusion criteria will be reviewed.

Prior to dosing (within 60 min before vaccination), the following activities will be completed:

- Vital signs, measured following 3 min rest (sitting BP, HR, RR and oral temperature);
- A blood sample for serology and safety laboratory testing (18 ml) will be drawn.
- Urine sample will be collected for safety testing.

Vaccine administration: Each subject will receive the injection as described in Section 7.3. The time and date of vaccination will be documented in the CRFs and on the CRC Drug Administration Records.

After vaccination: Subjects remain in the CRC for approximately 1 hour after injection. Vital signs (sitting BP, HR, respiratory rate, and oral body temperature) will be measured at 60 (± 15) minutes after treatment, and recorded as appropriate.

Before discharge from the CRC a study physician will examine the injection site using a grading score (Appendix C).

The subjects will then be released from the CRC following a study physician's approval.

6.1.3 Visit 3 - Second Vaccine Administration: Month 1, (Week 4± 3 days)

The second vaccination will take place 28 (±3) days after the first vaccination (Visit 2). The previous injection site will be inspected before the second administration. Procedures will be identical to Visit 2.

6.1.4 Visit 4 – Follow-up: Month 2 (Week 8± 3 days)

Subjects will arrive in the CRC and will be will be interviewed by the CRC study personnel regarding change in concomitant medications or changes to their health status since the last visit. A 10 ml blood sample for serology will be drawn and the subject will be released from the CRC.

6.1.5 Visit 5 – Follow-up: Month 3 (Week 12± 3 days)

Procedures will be identical to Visit 4.

6.1.6 Visit 6 – Follow-up: Month 4 (Week 16± 3 days)

Procedures will be identical to Visit 4.

6.1.7 Visit 7 – Follow-up: Month 5 (Week 20± 3 days)

Procedures will be identical to Visit 4.

6.1.8 Visit 8 - Third Vaccine Administration: Month 6, (Week 24± 3 days)

The third (last) vaccination will take place 5 months after the second vaccination (Visit 3). The previous injection site will be inspected before the second administration. Procedures will be identical to Visit 2.

6.1.9 Visit 9 – Follow-up: Month 7 (Week 28± 3 days)

Procedures will be identical to Visit 4.

6.1.10 Visit 10 – Follow-up: Month 9 (Week 36± 8 days)

Procedures will be identical to Visit 4.

6.1.11 Visit 11 – Study Termination: Month 12 (Week 48± 8 days)

The following assessments will be performed:

- Physical examination
- Vital signs: (sitting BP, HR, RR, oral temperature)
- 12-lead ECG
- Laboratory safety tests (See Appendix B)
- Serology tests
- AE and concomitant medication recording

The amount of blood drawn in this visit is approximately 23 ml.

The total amount of blood drawn for serology and routine safety laboratory tests will be about 168 ml over a period of 13 months.

6.2 UNSCHEDULED VISIT

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the Investigator due to medical considerations. The date and reason for the unscheduled visit will be recorded. AE monitoring and concomitant medication recording will be performed by the Investigator. Other procedures and evaluations will be completed as deemed necessary by the Investigator and may include (but not limited to) safety laboratory tests, ECG, vital signs and physical examination.

6.3 BLOOD SAMPLING FOR IMMUNOGENICITY

6.3.1 Serology Tests

The immunogenicity of the vaccine will be assessed by the anti-HBsAg, anti-preS1 and anti-preS2 antibody levels at each visit, from visit 2 till visit 11, as presented in Appendix A.

6.3.2 Blood Sampling and Processing.

Approximately 10 ml of blood will be collected in SST Gel tubes.

Processing and storage of the samples are detailed in the lab manual provided by the Sponsor.

6.3.3 Shipment of Samples to the Bioanalytical Laboratory

Samples will be shipped in a cold pack to the central laboratory on the same day it is drawn from the subject, as detailed in the lab manual provided by the Sponsor.

6.4 SAFETY ASSESSMENTS

Safety assessments will be based on AEs reported by the subject or observed by the Investigator, concomitant medication use, clinically significant changes from baseline of vital signs, ECG, physical examination, and safety laboratory tests (hematology, chemistry, and urinalysis).

6.4.1 Adverse Events (AEs)

AEs will be recorded continuously starting from the signing of the ICF through the Study Termination visit, in those subjects who have been actually dosed.

AEs reported prior to dosing will be recorded in the CRF and considered non-treatment emergent AEs. Any new systemic effect that occurs between scheduled visits should be brought to the attention of the Investigator and recorded in the subject's medical file and in the CRF.

6.4.2 Local reaction at injection site

Local reaction at injection site, based on the FDA Guidance to Industry[29] (see grading scale in Appendix C) will be assessed by a study physician on treatment visits.

6.4.3 Vital Signs

Vital signs (sitting systolic and diastolic blood pressure, heart rate, respiratory rate and oral temperature) will be measured after at least 3 minutes rest as per standard practice at the investigational site at the following time points:

- On screening,
- On each treatment visits (Visits 2, 3 and 8): within 60 minutes before vaccination, 60 (± 15) minutes after vaccination.
- On Study Termination visit

Changes in vital signs determined by the Investigator to be clinically significant will be noted as an AE on the appropriate CRF and in the subject's file. Such abnormalities will be closely monitored until stabilized or resolved.

6.4.4 Electrocardiogram (ECG)

A 12-lead ECG will be performed at the following time points:

- On screening,
- On Study Termination visit

6.4.5 Physical Examination

Complete physical examination will be performed at the following time points:

- On screening,
- On Study Termination visit

Significant changes from baseline examination on screening will be recorded as AEs in the CRF and in the subject's file.

6.4.6 Safety Laboratory Tests

Safety laboratory tests including biochemistry, hematology and urinalysis (see details in Appendix B) will be performed at the following times:

- On screening;
- On each treatment visits (Visits 2, 3 and 8): within 60 minutes before vaccination
- On Study Termination visit (without the screening serology tests)

All safety (chemistry, hematology urinalysis, serology and urine tests will be carried out by AML Laboratories, except urine test for pregnancy which will be performed at the trial site by the CRC staff.

Clinically significant laboratory tests or tests of unknown significance which are outside the normal range may be repeated as clinically indicated until the values return to normal, or until the etiology has been determined and the condition considered stable. Abnormal laboratory test results that are considered to be clinically significant by the investigator will be reported as an AE in the CRF.

7 INVESTIGATIONAL PRODUCTS

7.1 DESCRIPTION OF INVESTIGATIONAL PRODUCT

Sci-B-Vac™ is a recombinant Hepatitis B vaccine, produced by SciVac Israel Ltd. It contains the 3 surface antigens of the HBV: HBs, preS1 and preS2 antigens. Each 1ml dose contains sterile 10µg HBs antigen. It is formulated for intramuscular injection supplied in a single use vials containing 1 ml suspension. The components of the investigational vaccine are produced under aseptic conditions and according to the rules of current Good Manufacturing Practice and guidelines applicable to IMPs (investigational medicinal products). The vaccine lot used in this trial will be tested and released by the Quality Assurance Department of the Sponsor.

7.2 PACKAGING AND LABELLING OF INVESTIGATIONAL PRODUCT

All clinical supplies will be provided from the designated commercial batch packed and labeled in compliance with the Good Manufacturing Practices of drugs used in clinical trials and with the Israeli Ministry of Health Guidelines for Clinical Trials in Human Subjects. All study vaccines provided will be appropriately documented.

7.3 STUDY DRUG ADMINISTRATION

Sci-B-Vac™ Vaccine will be administered intramuscularly in the deltoid area of the arm, 10 µg/ml, on Month 0, 1 and 6.

Vaccine administration will be documented in the Case Report Forms and on the Drug Administration Records.

Upon loading the syringe by the nurse, with the vaccine, it should be administered to the subjects immediately.

7.4 SHIPMENT OF INVESTIGATIONAL PRODUCT

Prior to study start, study medications will be supplied to the CRC by the Sponsor. It is the responsibility of the Sponsor to ensure the vaccine is kept at 2-8°C during the shipment.

The Sponsor must notify the Investigator/study staff prior to dispatch of drug supplies, with the anticipated date of their arrival, addressed to:

Clinical Trials Unit
TASMC Pharmacy
Tel-Aviv Sourasky Medical Center
6 Weizmann Street,
Tel-Aviv 64239, Israel

Shipment of study drug supplies for the study will be accompanied by a shipment form describing the contents of the shipment drug information, acknowledgement of receipt and other appropriate documentation. The shipment form will assist in maintaining current and accurate inventory records.

7.5 RECEIPT AND STORAGE OF INVESTIGATIONAL PRODUCT

All study supplies should arrive at the Pharmacy in sufficient quantity and in time to enable dosing as scheduled.

The investigational product will be accompanied by a shipment form and appropriate documentation.

Vaccines will be stored at the hospital pharmacy in an appropriate locked room until dosing, refrigerated at an average temperature between 2ºC to 8ºC. During the storage at the pharmacy, the temperature of the refrigerator will be monitored continuously and recorded by a pharmacist or another member of study staff who will record refrigerator temperature log. The Sponsor should be notified for any deviation from the storage conditions. Vaccine vials should never be exposed to freezing temperatures.

The Investigator will issue a prescription, and the vaccines will be picked up from the pharmacy before administration. The vaccines will be transferred from the pharmacy to the CRC in an icebox. The time during which the vaccines will be out of the refrigerator should not exceed 15 min.

7.6 ACCOUNTABILITY OF INVESTIGATIONAL PRODUCT

The TASMC pharmacy will be responsible for recording the receipt of all drug supplies and for ensuring the supervision of the storage and allocation of these supplies. When a shipment is received, the pharmacist verifies the quantities received and the accompanying documentation and returns the acknowledgment of receipt to the Sponsor.

Drug administration will be recorded in the source documents, in the CRFs and in the Drug Administration Record form. The latter includes the subject identification, quantity (volume) and date of administration. The containers from which the drug was administered to the subjects will be retained for dose confirmation.

At the end of the study, delivery records of study drug will be reconciled with used / unused stocks and appropriate forms will be filled in, to verify that all used, unused or partially used supplies have been returned and that no study supplies remain in the Investigator's possession.

All unused drug supplies, partially used and empty containers will be returned to the Sponsor or disposed of according to the Sponsor's instructions.

8 STUDY RESTRICTIONS

8.1 CONCOMITANT MEDICATIONS

The following medications are prohibited for use by the subject throughout the study:

- Systemic corticosteroid treatment less than 14 days before first vaccination and throughout the study.
- Immunosuppressant medications (e.g. mycofenolate mofetil, cyclosporine, cyclophosphamide etc.)
- Biological immune-modifying agents (e.g. anti TNF alfa, anti CD20)

8.2 ADDITIONAL RESTRICTIONS

Women of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-HCG) test on screening (and negative consecutive urine tests during the study) and be willing and able to use an acceptable method of birth control (acceptable methods of birth control include: intrauterine devices, oral contraceptive, contraceptive patch, long-acting injectable contraceptive or double-barrier method - condom or diaphragm with spermicide) from the screening visit through the EOS visit, or declare that they are abstaining from sexual intercourse, or be surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or post-menopausal.

9 SAFETY AND PHARMACOVIGILANCE

9.1 ADVERSE EVENT DEFINITION

An AE is defined as "Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related".

An AE (also referred to as an adverse experience) can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality or seriousness. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

An abnormal result of diagnostic procedures including abnormal laboratory findings will be considered an AE if it fulfills one or more of the following:

- Results in subject's withdrawal by the Investigator
- Is associated with a serious adverse event (SAE)
- Is associated with clinical signs or symptoms
- Is considered by the physician to be of clinical significance (a laboratory abnormality that is not clinically significant will not be considered an AE)

A new condition or the worsening of a pre-existing condition will be considered an AE.

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Suspected adverse reaction is “any adverse event for which there is a reasonable possibility that the drug caused the adverse event.”

AEs do not include the following:

- Stable or intermittent chronic conditions (such as myopia requiring eyeglasses) that are present prior to study entry and recorded in the subject's file and do not worsen during the study
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if not present at baseline
- Overdose of either study drug or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred)
- Pregnancy alone is not considered an AE. Elective abortions without complications should not be handled as AEs.

All AEs, whether observed by the Investigator or designee or volunteered by or elicited from the subject, should be recorded individually in the CRF. AEs will be recorded from the time a subject has signed the ICF and throughout the study, including the follow up period, in those subjects who have been dosed at least once.

Severity of the AE will be assessed by the investigating physician in accordance with the definitions in Appendix C. An SAE must fulfill the requirements listed in the Section 9.2.

The Investigator will document in his/her opinion the relationship of the AE to the study drug using the criteria outlined in definition of adverse events relationship to study drug (Table 1).

Table 1: Definition of adverse events relationship to study drug

TERM	DEFINITION	CLARIFICATION
Unrelated	In general, this category can be considered applicable to those adverse events, which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug.	An adverse experience may be considered unlikely related if or when (must have two): • It does not follow a reasonable temporal sequence from the administration of the test drug. • It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • It does not follow a known pattern of response to the test drug. • It does not reappear or worsen when the drug is re-administered.
Possibly Related	This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration appears unlikely but cannot be ruled out with certainty.	An adverse experience may be considered possibly related if or when (at least two of the following): • It follows a reasonable temporal sequence from administration of the drug. • It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • It follows a known pattern of response to the test drug.
Probably Related	This category applies to those adverse events which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug.	An adverse experience may be considered probably related if or when (at least three of the following): • It follows a reasonable temporal sequence from administration of the drug. • It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • It follows a known pattern of response to the test drug.

Outcomes to Date are classified as follows:

- Recovered – The subject has fully recovered from the adverse event with no residual effects observable
- Recovered with sequelae – The subject has recovered from the adverse event with residual effects observable
- Recovering – the subject status improved but has been recovered
- Ongoing – AE is not recovered
- Fatal
- Unknown

AEs will be coded by Data Management using the using the Medical Dictionary for Regulatory Activities (MedDRA).

9.2 SERIOUS ADVERSE EVENTS (SAEs)

An SAE is any AE occurring at any dose that suggest a significant hazard or side effect, regardless of the Investigator or Sponsor's opinion on the relationship to the investigational product and that results in, but may not be limited to, any of the following outcomes:

- death (regardless of the cause)
- a life-threatening adverse event or suspected adverse reaction
- inpatient hospitalization or prolongation of existing hospitalization (any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility)
- a persistent or significant disability/incapacity or a substantial disruption of the ability to conduct normal life functions
- a congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be **serious** when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event.

Hospitalization for elective treatment of a pre-study condition that did not worsen while on study and optional hospitalizations not associated with a clinical adverse event (e.g., elective cosmetic surgery) are not considered SAEs.

Significant medical events are those which may not be immediately life-threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; resulting in an AE will normally be considered serious by this criterion.

A **life-threatening** adverse drug experience is any adverse event that places the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

9.3 DEFINITION OF AN UNEXPECTED ADVERSE EVENT

An **unexpected** adverse event is any adverse event, the specificity or severity of which is not consistent with information in the clinical protocol or current Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product (package inserts are available separately at the participating center).

Serious Unexpected Suspected Adverse Reaction (SUSAR) is a serious adverse reaction assessed as unexpected by the Sponsor and that is judged by either the reporting investigator or the Sponsor to have a reasonable causal relationship to a medical product.

9.4 NOTIFICATION OF SERIOUS OR UNEXPECTED ADVERSE EVENT

Per FDA new safety reporting requirements (US Department of Health and Human Services September 2010)[30] a sponsor must continue to "promptly" review all safety information obtained from foreign or domestic sources. However, the sources of information listed in the regulation has expanded to include "any clinical or epidemiological investigations, animal or *in vitro* studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

If the Investigator identifies a SAE or Unexpected AE, an SAE report form must be completed and sent within 24 hours of the Investigator's knowledge of the event to the sponsor. The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

These preliminary reports will be followed within 24 hours by more detailed descriptions that will include a completed SAE form, copies of hospital case reports (i.e., hospital progress notes, results of applicable diagnostic tests, lab results and biopsy results), autopsy reports, and other documents, when requested and applicable.

For regulatory purposes, initial SAE reports submitted to SciVac immediately and should include:

a) a suspected investigational medicinal product

b) an identifiable subject (e.g., study subject code number)

c) an adverse event with a seriousness and the Investigator's assessment of the relationship to study drug

d) an identifiable reporting source (investigator contact details)

Once faxed or emailed, the printed SAE form and accompanying documentation should be placed in the SAE section of the Investigator's site file.

In addition, all AEs/SAEs/SUSARs will be reported to the IRB/IEC and regulatory authorities as required by local regulations and ICH-GCP guidelines.

Follow-up of SAEs/SUSARs

Follow-up of SAEs/SUSARs that occur during the study will continue until their satisfactory resolution or stabilization. In outstanding cases, it may be defined as "ongoing without further follow-up" by the Investigator and Sponsor's decision.

When supplementary information is available, a follow-up SAE Report Form must be completed by the site (marked as "follow-up report") and reported as indicated above.

Information to include on SAE form

The following information should be provided in the SAE form to accurately and completely record the event:

Investigator name and site address

Subject study identification number

Subject's initials

Subject demographics (gender, date of birth or age, weight, height)

Clinical Event:

- Description
- Date and time of onset, stop date, or duration
- Severity
- Treatment (including hospitalization)
- Relationship to study drug (causality)
- Action taken regarding study drug
- Information on recovery and any sequelae
- If the AE resulted in death
  - Cause of death (whether or not the death was related to study drug)
  - Autopsy findings (if available)
- Medical History case report form (copy)
- Concomitant Medication case report form (copy)
- Any relevant reports (laboratory, discharge, etc.)

Accompanying documentation, such as copies of hospital case reports, autopsy report, and other documents when applicable, should be sent as soon as they are available.

Subsequent additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded by the site to the Sponsor representative and study monitor within 24 hours of the information becoming available.

SAEs should also be reported to the IRB/IEC according to local regulations.

Subjects who have had an SAE during the treatment period must be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained.

Any newly emergent SAE after treatment is discontinued or the subject has completed the study and is considered to be related to the study drug or study participation should be recorded and reported immediately. The post-study period for the purpose of SAE reporting is up to 30 days following last visit of the study.

Follow-up Reports for non-serious AEs

All AEs, that do not meet any of the criteria for serious, should be regarded as non-SAEs. All AEs must be followed until resolution or stabilization and will be recorded on the Adverse Event Record in the CRF and if relevant, the Concomitant Medications Record in the CRF. Severity and relationship to study drug will be assigned by the Investigator as described in the section above.

9.5 ANTICIPATED ADVERSE EVENTS

Previous human experience and known adverse effects of the test product are detailed in the Product Information leaflet.

10 STATISTICAL METHODOLOGY

A total of 84 subjects, are expected to be recruited into study. The trial will follow-up eligible subject for a total duration of 12 months. Two interim analyses are planned to be conducted at the time when approximately 65% subjects and 82.5% of the subjects will reach Month 7 or early terminated the study.

10.1 INTERIM AND FINAL ANALYSES

Two interim analyses are planned for possible early termination of the study. These analyses will be performed at the time when approximately 65% subjects and 82.5% of the subjects will reach Month 7 or early terminated the study. The first interim analysis will use an alpha level of 0.0109 and the second interim analysis will use an alpha level of 0.0239. The final analysis will use an alpha level of 0.0414 representing the use of the Lan-DeMets correction to type-I error due to multiple testing.

10.2 SIGNIFICANCE LEVEL

The overall significance level for this study will be 5% using two-tailed tests.

10.3 SAMPLE SIZE RATIONALE

Sample size determination was performed under the following assumptions:

- The primary endpoint for the study is the Seroprotection Rate (SPR), defined as the proportion of subjects with anti-HBs antibody titer at least equal to 10mIU/ml, at Month 7 (i.e. one month after the third immunization with Sci-B-Vac™). Subjects early terminated from the study for any reason at any time while having an anti-HBs antibody concentrations ≥ 10mIU/ml will be considered among those who met endpoint.
- It is expected that the true rate of SPR following treatment with Sci–B-Vac™ is 95% or more.
- The principal analysis of the primary endpoint will be a non-inferiority analysis testing the below hypothesis:
  - ✓ H_0: P-p_0 <= -Margin
  - ✓ H_1: P-p_0 > -Margin

- Where p0, the assumed true SPR is 95% and the non-inferiority margin is 12.5%, employing that study will be considered successful if the lower bound of the 95.86% exact CI (using the alpha level at final analysis) will be 82.5% or more (lower non-inferiority limit).
- Under these assumptions, sample of 70 subjects will provide a power of 86.1% or more to demonstrate that the observed SPR is non-inferior to the rate of 95%. Sample size is adjusted to a total of 84 subjects to account for an anticipated withdrawal rate of approximately 20%.

10.4 ANALYSES SETS

10.4.1 Modified Intent-to-Treat (mITT) Analysis Set

The Modified Intent-to-Treat (mITT) analysis set is a subset of the ITT set. This set will consist of all enrolled subjects who were vaccinated at least once with Sci-B-Vac™ and had at least one post study IP administration follow-up visit. This analysis set will serve as the primary analysis set for efficacy and safety inference.

10.4.2 Full Treatment (FT) Analysis Set

The Full Treatment (FT) analysis set is a subset of the mITT analysis set and will consist of all subjects who were vaccinated 3 times with Sci-B-Vac™ and had at least one visit following the 3rd vaccination.

10.5 SUBJECT DISPOSITION

Data from subjects who are screened but not treated, subjects in the mITT, FT analysis sets, as well as study withdrawal data will be summarized using descriptive statistics. This summary will include all subjects screened into the study. The denominator for calculating the percentages will be the set of the mITT.

10.6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and baseline data as well as disease prognostic factors, medical history and prior medications will be summarized for the mITT analysis set using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation (SD), standard error, median, minimum, and maximum) will be provided. For categorical variables, subject counts and percentages will be provided. Categories for missing data will be presented if necessary. Missing categories will be presented if necessary.

10.7 EFFICACY ENDPOINTS AND ANALYSES

Analyses of primary and secondary efficacy endpoints will use the mITT Analysis Set including all enrolled subjects who were vaccinated at least once with Sci-B-Vac™ and had at least one post first Sci-B-Vac™ administration follow-up visit.

10.7.1 Primary Endpoint Definition and Analysis

The primary endpoint of the study is the Seroprotection rate (SPR), defined as the proportion of subjects with anti-HBs antibody titer at least equal to 10mIU/ml, at Month 7 (i.e. one month after the third immunization with Sci-B-Vac™). Subjects early terminated from the study for any reason

at any time while having an anti-HBs antibody concentrations ≥ 10mIU/ml will be considered among those who met endpoint.

The principal analysis of the primary endpoint will employ a non-inferiority analysis [SAS PROC FREQ with binomial (noninf margin=.125 p=(1-α) exact)] statement will be used for testing the below hypothesis:

H_0: P-p_0 <= -Margin

H_1: P-p_0 > -Margin

Where p_0, the assumed true SPR is 95% and the non-inferiority margin is 12.5%, employing that study will be considered successful if the lower bound of the (1-α) exact CI will be 82.5% or more.

10.7.2 Secondary Endpoints and Analyses

The secondary endpoints for the study are:

- SPR at one month after the second injection of Sci-B-Vac™ (i.e. Month 2/visit 4).
- SPR at month 6 prior to the third injection of Sci-B-Vac™ (i.e. Month 6/visit 8).
- SPR at one month after the first injection of Sci-B-Vac™ (i.e. Month 1/visit 3).
- The geometric mean concentration (GMC) as determined by anti-HBsAg antibody titers at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.

SPR at all time points as above defined will be analyzed using the principal analysis method as above defined. The geometric mean concentration (GMC) as determined by anti-HBsAg antibody titers at Month 0, then at every month until Month 7 inclusive and at months 9 and 12 will be displayed across time in order to establish the kinetic of the immunological response during the study.

10.7.3 Exploratory Endpoints and analyses

The exploratory endpoints for the study are:

- The anti-preS1 antibody titers measured at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.
- The anti-preS2 antibody titers measured at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.

The geometric mean concentration (GMC) at Month 0, then at every month until Month 7 inclusive and at months 9 and 12 will be displayed across time in order to establish the kinetic of the immunological response during the study.

10.8 DESCRIPTIVE STATISTICS

All measured variables and derived parameters will be listed individually and tabulated and descriptive statistics will be provided. For categorical variables summary tables will be provided displaying sample size, absolute and relative frequency and percentages. For continuous variables summary tables providing sample size, mean value or geometric means where appropriate, median, standard deviation (SD), standard error, minimum and maximum values. Summary statistics of Anti-HBs antibody concentrations and Anti-PreS1 and Anti-PreS2 antibodies concentrations will use geometric means due to the expected dispersion and skewness of the data.

Descriptive statistics for each of the study endpoints will be provided for the mITT Analysis Set and for both mITT and FT analyses set for the primary endpoint only.

10.9 SAFETY ASSESSMENTS

10.9.1 Treatment Emergent Adverse Events

Adverse events will be recorded from the time when a subject has signed the Informed Consent Form and throughout the study, including the follow-up period. The MedDRA dictionary will be used to standardize the terms used by the investigator to describe the Adverse Events. The following were incorporated into the analyses which will include only Treatment Emergent Adverse Events (TEAEs), namely, events that were started on the day of first study dose or afterwards.

- The incidence (no. of patients) and frequency (no. of events) of TEAEs broken down by SOC and by SOC and Preferred Term according to MedDRA dictionary.
- The incidence (no. of patients) and frequency (no. of events) of TEAEs broken down by events attributes.
- The derived dictionary used in the analyses.
- Listing of SAEs (regardless if started before or after first study dose) of randomized and dosed subjects captured in the clinical database until database drop date.
- Listing of Non-Treatment Emergent AEs.

10.9.2 Vital Signs

Vital signs will be measured at each treatment visit including at unscheduled or early termination visits. Analyses of vital signs were performed in the following manner:

- Box-Plots of vital signs before first study dose and afterwards by scheduled visit will be generated.
- Descriptive statistics of vital signs before first study dose and afterwards as well as the changes from baseline by scheduled visit will be generated.
- The incidence (no. of subjects) of potentially clinically significant (PCS) abnormal values will be summarized in a frequency table and will be listed.

10.9.3 Laboratory Evaluations

Analyses of safety laboratory data will be performed in the following manner:

- Box-Plots of laboratory measurements first study dose and afterwards by scheduled visit will be provided.
- Descriptive statistics of quantitative tests results and changes from baseline by scheduled visit.
- Quantitative laboratory measurements will be categorized with reference to the normal ranges as Low, Normal or High. Shift analysis of the categorical change form baseline to each scheduled visit and to the last observed assessment will also be presented.
- Incidence tables of PCS lab values as well as the individual subject listing will also be provided.

10.9.4 Other Safety Outcome Measures

Summary statistics of other safety evaluations including assessment of local safety evaluations and pain evaluations will be tabulated and listed. Kaplan-Meier curves will be used to describe time to study withdrawal.

10.10 Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the clinical study report, or any combination of these, as appropriate.

10.11 Statistical Software

Study accumulated data will be analyzed and summarized using the SAS® version 9.4 (SAS Institute, Cary North Carolina) or higher.

11 ETHICS

11.1 Institutional Review Board or Independent Ethics Committee

Prior to initiation of the study, the Investigator will submit the study protocol and amendments, sample ICF, and any other documents that may be requested to the IRB/IEC for review and approval. The Investigator will request that the IRB/IEC provide written approval of the study and will keep on file records of approval of all documents pertaining to this study. The Investigator will not begin the study until the protocol and ICF have been approved by the IRB/IEC. The Investigator must agree to make any required progress reports to the IRB/IEC, as well as reports of SAEs, life-threatening conditions, or death.

11.2 Ethical Conduct of the Study

All clinical work conducted under this protocol is subject to GCP guidelines. This includes an inspection by Sponsor or its designee, health authority or IRB/IEC representatives at any time. The Investigator must agree to the inspection of study-related records by health authority representatives and/or Sponsor or its designee.

The study will be conducted in accordance with Sponsor's standards operating procedures and the following guidelines:

- GCP: Consolidated Guideline (International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- Declaration of Helsinki: Seoul, 2008
- Israeli Guidelines, Laws and Regulations for the conduct of clinical trials (2006)

11.3 Subject Information and Consent

Prior to screening for the study each subject will be informed in detail about the study drugs to be administered, and the nature of the clinical investigation with its risks and discomforts to be expected. The basic elements of informed consent as specified by the FDA (21 CFR 50.25) and ICH-GCP will be followed. The subjects will also be instructed that they are free to withdraw their

consent and discontinue their participation in the study at any time without prejudice. Written consent will be obtained from each subject to be involved in the clinical trial by using the IRB/IEC-approved ICF prior to the conduct of any study-related activity. A copy of the ICF will be submitted together with this protocol and must be approved by the IRB/IEC prior to study commencement. Each subject will be given a copy of the written ICF, and each subject's chart will include the signed ICF for study participation. The original subject signed and dated ICFs will be maintained by the site for 15 years. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having done so during the study.

11.4 SUBJECT INSURANCE

A product liability to cover against injury and damages arising from the use of products in this project is provided by SciVac for the total duration of the study covering the subjects and Investigators in respect of the risks involved in conducting this study according to this protocol. The insurance policy will be filed in the Investigator's site file or can be made available to the Investigator and to the IRB/IEC upon request.

Where applicable, subjects will be insured through contract between an insurance company and the Sponsor.

11.5 PERSONAL DATA PROTECTION

SciVac complies with the principle of subject's right to protection against invasion of privacy. Throughout this trial, all subject data will be identified only by a subject identification number and subject initials and date of birth. The data will be blinded in all data analyses. The subject must be informed and consent as required that authorized personnel on behalf of SciVac such as study monitor, auditor etc. and relevant health regulatory agency will have direct access to personal medical data to assure a high quality standard of the study.

At the subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

11.6 INFORMING THE GENERAL PRACTITIONER

The Investigator will inform the subject's primary care physician of the subject's participation in the study, by sending a letter to the physician as required by the Israeli Guidelines for the Conduct of Clinical Trials.

11.7 PROTOCOL EXCEPTIONS AND DEVIATIONS

It is expected that subjects will meet all eligibility criteria as specified in the protocol. Deviations from the protocol should be avoided, unless required for the safety of the subject. Protocol deviations, and if possible the reason for occurrence, will be documented by the study monitor and will be included in the final clinical study report. The Investigator must report any protocol deviation to the Sponsor and if required, to the IRB/IEC in accordance with local regulations, within reasonable time.

11.8 PROTOCOL AMENDMENTS

All protocol modifications must be submitted to the site IRB/IEC in accordance with local requirements and, if required, to the Regulatory Authority, either as an amendment or a notification.

Approval for amendments must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the changes involve only logistical or administrative aspects of the trial. No approval is required for notifications.

12 QUALITY CONTROL AND QUALITY ASSURANCE

The study will be conducted according to GCP as outlined by ICH Topic E6 step 5 guidelines. The Sponsor maintains a quality assurance system with written SOPs to ensure that clinical trials are conducted and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements.

12.1 AUDITS AND INSPECTIONS

The study may be audited according to the Sponsor's QA inspection program. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with study protocol and ICH GCP guideline. Audit visit(s) will be arranged in advance with site personnel at a mutually acceptable time.

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor quality assurance or its designees or to regulatory authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents. These audits or inspections may take place at any time, during or after the study, and are based on the national regulations, as well as ICH guidelines.

12.2 STUDY MONITORING

Monitoring of the study is the responsibility of the Sponsor and may be delegated to a CRO or a contract monitor. The study monitor will advise the Investigator regarding the practical conduct of the study and maintaining compliance with the protocol, GCP and all applicable regulatory requirements.

Before study initiation, at a site initiation visit or at an Investigator's meeting, a CRO representative will review the protocol and CRFs with the Investigator and his staff.

Throughout the course of the study, the study monitor will oversee the conduct and the progress of the study by frequent contacts with the Investigator. This will include telephone calls and on-site visits. During the on-site visits, the CRF will be reviewed for completeness with corresponding source documents. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor will also perform drug accountability checks and may periodically request review of the Investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Periodically, some or all of the facilities used in the study (e.g., local laboratory, pharmacy) may be reviewed. Monitoring visits will be arranged in advance with site personnel at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the monitor to review CRFs and relevant source documents. The Investigator should be available to answer questions or resolve data clarifications. The Investigator or appointed delegate will receive the study monitor during these on-site visits, cooperate in providing the documents for inspection, and respond to inquiries.

The Investigator will ensure that the study participants are aware of and consent that personal information may be scrutinized during the data verification process as part of study-related

monitoring and auditing by properly authorized persons associated with SciVac or inspection by domestic and/or foreign regulatory authority(ies). However, participation and personal information should be treated as strictly confidential to the extent that the applicable law permits and not be publicly available.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

12.3 QUALITY LABORATORY STANDARDS

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the local institution laboratory and central laboratories.

Before the study begins, the laboratories to be used in the study will provide a list of the reference ranges for all laboratory tests to be undertaken and details of the method used for quality control. These will be held in the Investigator file and the trial master file. The methods employed for each assay should be available on request. Any change in the laboratory, its procedures, references, values, etc. during the study must be notified promptly to the Sponsor.

12.4 STUDY DOCUMENTATION

Study documents will include the following:

- Signed ICFs
- Source documents (e.g., subject files, medical notes, study worksheets)
- Investigator copies of the CRFs and SAE reports
- Investigator site file + contents
- Laboratory manual

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

12.4.1 Source Document

The Investigator will permit study-related monitoring, audits by or on behalf of the Sponsor, IRB/IEC review and regulatory inspections providing direct access to source data documents. Source documents are original records in which raw data are first recorded. These may be office/clinic/hospital records, charts, diaries, ultrasound images, and laboratory results, ECG printouts, pharmacy records, care records, completed scales for each study participant and/or worksheets provided by the Sponsor. Source documents should be kept in a secure and limited access area. All source documents must be accurate, clear, unambiguous, permanent and capable of being audited. They should be made using a permanent form of recording (ink, typing, printing, optical disc, etc.). They should not be obscured by correcting fluid or have temporary attachments (such as removable self-stick notes). Source documents that are computer generated and stored electronically must be printed, signed and dated by the Investigator.

Source data for subjects registered to the study should indicate date ICF was signed, participation in clinical protocol number and title, treatment number, evidence that inclusion/exclusion criteria have been met.

12.4.2 Recording of Data on Case Report Form (CRF)

Case report forms are provided for each subject in electronic format.

The study data will be transcribed by study personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in CRF prepared by the sponsor. Data must be entered into CRF in English. Designated site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

Every effort should be made to ensure that all subjective measurements (eg, pain scale information or other questionnaires) to be recorded in the CRF are completed by the same individual who made the initial baseline determinations. The investigator must verify that all data entries in the CRF are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the study staff must adjust the CRF and complete the query.

If corrections to CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Site manager can generate a query for resolution by the study staff
- Clinical data manager can generate a query for resolution by the study staff

12.4.3 Investigator Site File

All documents required for the conduct of the study as specified in the ICH-GCP guidelines will be maintained by the Investigator in an orderly manner and made available for monitoring and/or auditing by the Sponsor and regulatory agencies.

12.5 CLINICAL TRIAL SUPPLIES

The Sponsor will be responsible for the supplying, administrating, inventory, and accountability of all clinical trial supplies, exercising accepted medical and pharmaceutical practices. An accurate and timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection upon request. Upon completion or termination of the study, the Investigator will keep the remaining clinical supplies along with a copy of the inventory record and a record of the clinical supplies returned. **Under no circumstances will the Investigator allow the study drugs to be used other than as directed by this protocol.**

Clinical trial supplies include, however, not limited to: CRF, study worksheets, lab supplies and study drug.

12.6 DATA MANAGEMENT

The CRF data will be captured within a clinical data management system (CDMS) that is 21 CFR part 11 compliant. The CDMS will be fully validated prior to use on the study to ensure that it meets the scientific, regulatory, and logistical requirements of the study. All CDMS users will be provided system and study specific training prior to use. Once trained, users will be provided with individual system access rights.

13 STUDY ADMINISTRATION

13.1 REQUIRED DOCUMENTS PRIOR TO STUDY INITIATION

Prior to the start of this study, all pre-investigational requirements must be met by the Investigator and study site. These may include:

- Appropriate local health authority documentation properly signed and dated by the required Investigator (i.e., the submission package)
- Signed copy (original) of the approved protocol
- Completed and signed statement of Investigator
- A signed Clinical Trial Agreement
- Curriculum vitae for the Investigator and sub-Investigator (can be collected at site initiation visit)
- IRB/IEC name and address; and membership list (can be collected at site initiation visit)
- Letter of approval from the IRB/IEC for both protocol (identified by protocol title and number) and ICF (identified by protocol title and number)
- Copy of the IRB/IEC-approved written ICF to be used in the study (that has also been approved by the Sponsor)
- Provisions for direct access to source/data documents if necessary for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection
- Name and location of the laboratory utilized for laboratory assays, and other facilities conducting tests, as well as a copy of the laboratory certificate and list of normal laboratory values (can be collected at site initiation visit)

In case a laboratory certification is not available, a written statement as to how the laboratory complies with quality assurance should be provided.

Upon satisfactory receipt of all required regulatory documents, Sponsor will arrange that study drugs be delivered to the study site. Supply of all other study materials will be the responsibility of SciVac and/or designee. Subject entry should not begin until after the required regulatory documents are confirmed as received and the Investigator Meeting/Initiation Meeting has occurred. All personnel expected to be involved in the conduct of the study will undergo orientation to include review of study protocol, instructions for CRF completion, AE reporting, and overall responsibilities including those for drug accountability and study file maintenance.

The Investigator and/or designee (study monitor) will prepare an Investigator's site file. This file should be used for all trial related documents. The Investigator will be responsible for keeping the

Investigator's site file updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

13.2 STUDY COMPLETION

This study is expected to end when all required subjects have been enrolled and the last subject has completed the study and the query resolution has been completed.

Data and materials that are required before the study can be considered complete and/or terminated are:

- Laboratory findings, clinical data, and all special test results from screening through the end of the follow-up period
- CRF (including correction forms) properly completed by appropriate study personnel and electronically signed by the Investigator
- Completed Drug Accountability Records
- Statement of outcome for each SAE reported
- Copies of protocol amendments and IRB/IEC as well as relevant health authority approval/notification (if applicable)

13.3 CLINICAL STUDY REPORT

A clinical study report will be issued by the Sponsor at completion of data analysis. This report will be a clinical and statistical integrated report, according to the ICH E3 guidelines.

13.4 RETENTION OF STUDY RECORDS

The Investigator will retain copies of the approved protocol, completed CRF, ICFs, relevant source documents, and all other supporting documentation related to the project for 15 years in a secure and safe facility with limited access. If the Investigator is unable to retain the study documents for the required amount of time, Sponsor or designee must be informed of the individual who will be assuming this responsibility.

Further retention, if required, will be negotiated at the end of this 15 year period. In that case, SciVac will notify, in writing, the Investigator when the clinical study data may be discarded. The Investigator will take measures to prevent accidental or premature destruction of these documents.

These files must be made available for inspection upon reasonable request by authorized representatives of Sponsor and/or the relevant regulatory agencies.

13.5 CONFIDENTIALITY AND PUBLICATION OF STUDY DATA

All information, including but not limited to information regarding Sci-B-Vac™ or the sponsor's operations (e.g., patent applications, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by or on behalf of the sponsor to the investigator and not previously published, and any data and results, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes or disclose it to others without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of Sci-B-Vac™, and thus may be disclosed as required to other clinical investigators and regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data and results generated in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data generated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data, results or reports that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

The sponsor shall have the right to publish such data, results and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will delete confidential or proprietary information of the sponsor (except for the results) and shall withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor may suggest reasonable changes to the publication but will not mandate modifications to scientific content and does not have the right to suppress publication of the results of the study. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version. The publication shall adequately acknowledge and appropriately reflect the contribution of the researchers and employees of each of the sponsor and the trial site and the source of the information included therein, in accordance with customary scientific practice.

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APPENDIX A

STUDY FLOW CHART

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Visit Name	**Screening**	**Treatment 1**	**Treatment 2**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**	**Treatment 3**	**Follow-up**	**Follow-up**	**Study Termination**
Month (Week) of the Study	***-1 ((-)4) - 0***	***0 (0)***	***1(4[1])***	***2(8[1])***	***3(12[1])***	***4(16[1])***	***5(20[1])***	***6(24[1]()***	***7(28[1])***	***9(36[2])***	***12(48[2])***
Activity											
ICF	X										
Demographics	X										
Inclusion/Exclusion	X	X									
Medical history	X										
Vital signs[3]	X	X[4]	X[4]					X[4]			X
Weight, height, BMI	X										
Physical examination	X										X
Blood safety tests[5]	X	X[6]	X[6]					X[6]			X
Screening serology[7]	X[8]										
General urinalysis	X	X[6]	X[6]					X[6]			X
Serum β-HCG	X										
Urine pregnancy test		X[6]	X[6]					X[6]			X
12-lead ECG	X										X
Sci-B-Vac™ injection[9]		X	X					X			
Local reaction grading		X[6]	X[6]					X[6]			
Serologic markers for hepatitis B infection	X[8,10]	X[6,11]	X[6,11]	X[11]	X[11]	X[11]	X[11]	X[6, 11]	X[11]	X[11]	X[12]
Serologic response to immunization[13]		X	X	X	X	X	X	X	X	X	X
Adverse Events	Recorded throughout the study										
Concomitant Medications	Recorded throughout the study										

[1] ± 3 days

[2] ± 8 days

[3] Sitting BP, HR, RR, oral temperature

[4] Within 60 min before vaccine administration and at 60 (± 15) min after vaccination

[5] CBC, blood chemistry, PT/INR (screening only) - see Appendix B

[6] Prior to vaccine administration

[7] Anti HIV (Ab type 1&2), anti-HCV Ab, anti-HAV IgM antibodies, ANA (See Appendix B)

[8] Positive serology excludes from participation in the study

[9] One IM injections of 1.0 ml into the deltoid muscle. The previous injection site will be inspected before the second and third administration.Subjects will remain for observation in the CRC for at least 1 hour after injections.

[10] HBsAg, anti-HBs antibodies, total anti-HBc antibodies and IgM anti-HBc antibodies.

[11] HBsAg only.

[12] HBsAg, Total anti-HBc antibodies and IgM anti-HBc antibodies

[13] Anti-HBsAg, anti-preS1 and anti-preS2 antibodies

APPENDIX B

LABORATORY SAFETY TEST PARAMETERS

LABORATORY SAFETY TEST PARAMETERS - SCREENING

SERUM BIOCHEMISTRY

- Total Protein
- Albumin
- Total bilirubin
- ALT
- AST
- GGT
- LDH
- CPK
- Alkaline phosphatase
- Glucose
- Sodium
- Potassium
- BUN
- Creatinine

HAEMATOLOGY

- Red Blood Cell Count
- Hemoglobin (HGB)
- Hematocrit (HCT)
- Mean Cell Hemoglobin (MCH)
- Mean Cell Hemoglobin Concentration (MCHC)
- Mean Corpuscular Volume (MCV)
- White Blood Cell (WBC) Count and Differential
- Platelet Count
- PT/INR

URINALYSIS

- Protein
- Nitrates
- Glucose
- Specific Gravity
- Ketones
- Urobilinogen
- Bilirubin
- pH
- Blood (Hemoglobin)
- Leukocytes
- Erythrocytes

SEROLOGY

- Human immunodeficiency virus (anti HIV Ab type 1&2)
- Hepatitis C virus (anti-HCV Ab)
- Hepatitis A virus (anti-HAV IgM antibodies)
- Antinuclear antibodies (ANA)
- Anti-HBs antibodies
- HBsAg
- Total anti-HBc, IgM anti-HBc antibodies

BLOOD PREGNANCY TEST

LABORATORY SAFETY TEST PARAMETERS – INTERIM AND STUDY TERMINATION

SERUM BIOCHEMISTRY

- Total Protein
- Albumin
- Total bilirubin
- ALT
- AST
- GGT
- LDH
- CPK
- Alkaline phosphatase
- Glucose
- Sodium
- Potassium
- BUN
- Creatinine

HAEMATOLOGY

- Red Blood Cell Count
- Hemoglobin (HGB)
- Hematocrit (HCT)
- Mean Cell Hemoglobin (MCH)
- Mean Cell Hemoglobin Concentration (MCHC)
- Mean Corpuscular Volume (MCV)
- White Blood Cell (WBC) Count and Differential
- Platelet Count

URINALYSIS

- Protein
- Nitrates
- Glucose
- Specific Gravity
- Ketones
- Urobilinogen
- Bilirubin
- pH
- Blood (Hemoglobin)
- Leukocytes
- Erythrocytes

URINE PREGNANCY TEST

APPENDIX C

TOXICITY GRADING SCALE TABLES

The following tables are based on the " FDA Guidance to Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"[29]

TABLE 1: GRADING OF LOCAL REACTION

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
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 2: GRADING OF VITAL SIGNS

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

TABLE 3: GRADING OF SYSTEMIC SYMPTOMS

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 gms/24 hours	4 – 5 stools or 400 – 800 gms/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
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

APPENDIX D

Sci-B-Vac™ PRODUCT LEAFLET

Sci-B-Vac™

Hepatitis B Vaccine (rDNA)

Description

Sci-B-Vac [Hepatitis B Vaccine (rDNA)] is a third generation vaccine produced by culture in Chinese hamster ovary cells. It consists of 22 nm particles isolated and purified from culture medium. The particles contain all three epitopes of hepatitis B surface antigen (HBsAg), namely S, pre-S_1 and pre-S_2, in their glycosylated and non-glycosylated forms, embedded in a phospholipid matrix, thus resembling the authentic plasma derived HBsAg. The antigen is formulated by adsorption onto aluminum hydroxide. The final preparation is virtually free of DNA and contains less than 3% protein contaminants. It does not contain any known animal viruses, bacteria or *Mycoplasma*.

Composition:
Active ingredient:
Sci-B-Vac 10μg/ml contains hepatitis B surface antigen 10μg/ml
Sci-B-Vac 5μg/0.5ml contains hepatitis B surface antigen 5μg/0.5ml
Sci-B-Vac 2.5μg/0.5ml contains hepatitis B surface antigen 2.5μg/0.5ml
Other ingredients:
$Al(OH)_3$ (2% solution) 0.5ml/1ml equivalent to dry weight of 1.5mg $Al(OH)_3$ per mL,
NaCl, KCl, $Na_2HPO_4 \times 12H_2O$, KH_2PO_4, WFI.

Each batch of the vaccine is rigorously tested for purity, safety, sterility and potency.

In each formulation, the HBsAg is adsorbed onto approximately 0.5 mg of aluminum per ml of vaccine.

Indications and Usage

Sci-B-Vac is indicated for active immunization against hepatitis B virus (HBV) infection.
Immunization against hepatitis B is expected, in the long term, to reduce not only the incidence of the disease,,but also its chronic complications such as massive hepatic necrosis, cirrhosis of the liver and hepatocellular carcinoma.

Vaccination with Sci-B-Vac is recommended for all ages in those subjects who are or will be at increased risk of infection with HBV. In areas of high prevalence of infection, the majority of the population is at high risk, especially neonates and children. In high risk areas, infection occurs primarily through mother to child and horizontal transmission. Therefore, vaccination should be targeted to prevent such transmission. In areas of intermediate and low prevalence, vaccination is recommended for neonates, infants and adolescents, as well as subjects who are or will be at increased risk of infection, such as:

- Health care personnel
  - Frequent recipients of blood products
  - Infants born to HBsAg-positive mothers
- Personnel and residents of public health institutions
- Persons at increased risk of the disease due to their sexual practices
  - Travelers to areas with high endemicity of HBV
  - Persons originating from areas of high endemicity
  - Users of illicit injectable drugs
- Military personnel, police personnel and anybody who through their work or personal lifestyle may be exposed to HBV
- Family members and others in intimate contact with persistent HBsAg-positive individuals.

Persons who develop anti-HBs antibodies following active infection with the hepatitis B vaccine are protected against the disease if they are re-exposed to the virus.

Clinical trials have shown that Sci-B-Vac induced protective levels of antibody in up to 100% of healthy adults who received the recommended three-dose regimen of 10 μg/dose.

Sci-B-Vac is highly immunogenic in children. The specific antibody titers tend to be an order of magnitude higher in children than in adults when the recommended doses are administered. Children tend to achieve seroprotection more frequently than adults.

Contraindications

Sci-B-Vac should not be administered to subjects with known hypersensitivity to any components of the vaccine or to subjects who developed symptoms suggestive of hypersensitivity after the injection of Sci-B-Vac.

As with other vaccines, the administration of Sci-B-Vac should be postponed in subjects suffering from acute severe illness. The presence of a minor infection, however, is not a contraindication for immunization..

Warnings

Due to the long incubation period for hepatitis B, it is possible for unrecognized infection to be present at the time of vaccination. Vaccination may not prevent hepatitis B in such individuals. The vaccine will not prevent infection caused by other agents such as hepatitis A, hepatitis C and hepatitis E or other pathogens known to infect the liver.

Precautions

General: As with any vaccine, epinephrine should be available for immediate use should an anaphylactic reaction occur.

Caution and appropriate care should be exercised in administering the vaccine to individuals with severe compromised cardiopulmonary status or to others in whom a febrile or systemic reaction could pose a significant risk.

Sci-B-Vac should under no circumstances be administered intravenously.

Pregnancy and Nursing Mothers: Animal reproduction studies have not been conducted with the vaccine. It is also not known whether the vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. The vaccine should be given to a pregnant woman only if clearly needed. It is not known whether the vaccine is excreted in human milk. Since many drugs are excreted in human milk, caution should be exercised when the vaccine is administered to a nursing woman.

Pediatric Use: Sci-B-Vac has been shown to be well tolerated and highly immunogenic in infants and children of all ages. Newborns also respond well; maternally transferred antibodies do not interfere with the active immune response to the vaccine.

Adverse Reactions

Sci-B-Vac is generally well tolerated. No serious adverse reactions attributable to the vaccine have been reported during the course of clinical trials. As with any vaccine, there is the possibility that broad use of the vaccine could reveal adverse reactions not observed in clinical trials.

In a series of studies, 2313 doses of Sci-B-Vac were administered to 771 healthy adults who were monitored for 5 days after each dose. The following adverse reactions were reported:

Incidence Equal to or Greater Than 1% of Injections:
Local Reaction (Injection Site): Injection site reactions consist of soreness and include pain, tenderness, pruritus, erythema, ecchymosis, swelling, warmth and nodule formation. These reactions were mild and resolved within two days after vaccination.

Additional complaints included fatigue/weakness, headache, fever (37.8ºC), malaise, nausea, diarrhea pharyngitis and upper respiratory infection.

Incidence Less Than 1% of Injections:
Sweating, aching, sensation of warmth, light-headedness, chills, flushing, vomiting, abdominal pains/cramps, dyspepsia, diminished appetite, rhinitis, influenza, cough, vertigo/dizziness, paresthesia, pruritus, rash (non-specified), angioedema, urticaria, arthralgia including monarticular, myalgia, back pain, neck pain, shoulder pain, neck stiffness, lymphadenopathy, insomnia/disturbed sleep, earache, dysuria and hypotension.

Dosage and Administration

Sci-B-Vac is a sterile suspension for intramuscular injection.

Adult Formulation, 10 µg/ml: each 1 ml dose contains 10 µg hepatitis B surface antigen; recommended for children above the age of 10 years and adults.

Pediatric Formulation (option 1) 2.5 µg/0.5 ml: each 0.5 ml dose contains 2.5 µg hepatitis B surface antigen; recommended for neonates, infants and young children.

Pediatric Formulation (option 2) 5 µg/0.5 ml: each 0.5 ml dose contains 5 µg hepatitis B surface antigen; recommended for neonates, infants and young children in highly endemic areas.
In each formulation, the hepatitis B surface antigen is adsorbed onto approximately 0.5 mg of aluminum per ml of vaccine.

Method of Administration: Sci-B-Vac should be injected intramuscularly into the deltoid muscle in adults and children or in the anterolateral thigh in neonates, infants and young children. The vaccine may be administered subcutaneously to persons who are at high risk of hemorrhage due to thrombocytopenia or bleeding disorders. Do not inject into the gluteal muscle.

Vaccination Schedule: The vaccination regimen for all subjects consists of three (3) doses of vaccine given according to the following schedule: first dose at elected date; second dose 1 month after the first dose; third dose 6 months after the first dose.
Booster Dose: The duration of the protective effect of Sci-B-Vac against HBV is unknown at present. A booster dose may be considered when the anti-HBs titer falls below 10 mIU/ml.

As with all parenteral drug products, the vaccine should be inspected visually for any particulate matter and/or discoloration prior to administration.
Before use of Sci-B-Vac, the vaccine should be shaken well to obtain a slightly opaque, white suspension. Discard if the contents of the vial appear otherwise. As with other vaccines, a dose of vaccine should be withdrawn under aseptic conditions and precautions taken to avoid contamination of the contents.

Recommended Storage Conditions:

The vaccine should be stored in the dark at +2°C to +8°C. **Do Not Freeze.**

Manufactured and Distributed by:
SciVac
Gad Feinstein Rd, Rehovot, Israel 7610303, P.O.Box 580 Tel: 972-8-9480666, Fax: 972-8-9480660

The format of this leaflet was determined by the Israeli Ministry of Health and its contents checked and approved.
Approved leaflet February, 2009.

16.1.1.2 Protocol V2 amendment 1

CLINICAL STUDY PROTOCOL

AN OPEN LABEL, SINGLE ARM, SINGLE CENTER CLINICAL STUDY IN HEALTHY SUBJECTS TO QUALIFY AN IN-HOUSE REFERENCE STANDARD BATCH OF SCI-B-VAC™

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Protocol Number: SciB018

CRC No. TRC 075/10217

Institutional Review Board Tel Aviv Sourasky Medical Center, Tel Aviv

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Version and Date: Version 2.0, September 9 , 2015

Amendment 1

PROTOCOL SIGNATURE PAGE

Title: An Open Label, Single Arm, Single Center Clinical Study in Healthy Subjects to Qualify an In-House Reference Standard Batch of Sci-B-Vac™

I declare that I have read and understood this study protocol. I agree to abide by this protocol (subject to any amendments agreed in writing between the Sponsor and Principal Investigator). Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of the subjects.

STUDY SPONSOR:

DR. NATHALIE MACHLUF, Ph.D.
Director of Regulatory and Clinical Affairs
SciVac Ltd .

Signature:

Date: 09 September 2015

PRINCIPAL INVESTIGATOR:

DR. JACOB ATSMON, M.D.
Clinical Research Center
Tel-Aviv Sourasky Medical Center

Signature:

Date: 9 Sep 2015

PROTOCOL SYNOPSIS

Study Title	**An Open Label, Single Arm, Single Center Clinical Study in Healthy Subjects to Qualify an In-House Reference Standard Batch of Sci-B-Vac™**
Protocol Number	SciB018
CRC Number	TRC 075/10217
Investigational Product	Sci-B-Vac™
Dosage Form	A single use vial containing 1 ml suspension.
Mode and schedule of Administration:	10 µg (in 1 ml) injected intramuscularly into the deltoid muscle. Three Intramuscular injections: on time-0, Month-1 and Month-6
Clinical Phase	IV
Study Objectives	**Primary objective:** To validate the new in-house reference standard vaccine for routine quality control purposes, in compliance with the European Pharmacopeia and the Israeli Ministry of Health. **Secondary objectives:** 1. To characterize the immunological response throughout the study. 2. To monitor the subjects for safety throughout the study period. **Exploratory objectives:** 1. To collect blood samples for the *in vitro* validation of anti-HBs, anti-preS1 and anti-preS2 antibodies assays. 2. To assess the anti-preS1 and anti-preS2 antibodies responses upon vaccination. 3. To investigate additional protective mechanisms of action and the type of immune response triggered by the vaccination. No genetic tests will be performed.
Efficacy Endpoints	**Primary endpoint:** Seroprotection rate (SPR), defined as the proportion of subjects with anti-HBs antibody titer at least equal to 10mIU/ml, at Month 7 (i.e. one month after the third immunization with Sci–B-Vac™). Subjects early terminated from the study for any reason at any time while having an anti-HBs antibody concentrations ≥ 10mIU/ml will be considered among those who met endpoint. **Secondary endpoints:** 1. SPR one month after the first injection and at every month until Month 6 inclusive and at months 9 and 12. 2. Percentage of subjects with anti-HBs antibodies titer ≥ 100mIU/ml at Month 0, and then at every month until Month 7 inclusive and at months 9 and 12.

	3. The geometric mean concentration (GMC) as determined by anti-HBsAg antibody titers at Month 0, then at every month until Month 7 inclusive and at months 9 and 12. **Exploratory endpoints:** • The anti-preS1 antibody titers measured at Month 0, then at every month until Month 7 inclusive and at months 9 and 12. • The anti-preS2 antibody titers measured at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.
Study Design and Procedures	This is an open label, single arm, single center clinical study in healthy subjects, who were never vaccinated against Hepatitis B and who are HBs antigen, anti-HBc and anti-HBsAg antibodies seronegative. Eligible subjects will be vaccinated 3 times with 10 mcg/ml of Sci-B-Vac™ according to the immunization schedule. The study will consist of three periods: • Screening period: Up to 4 weeks prior to first vaccination • Treatment and follow-up period: 6 months • Post-vaccination follow-up period: 6 months Blood samples will be collected prior to the first vaccination (Month 0), every month until month 7 inclusive, at Month 9 and at Month 12. Safety parameters will be assessed as outlined below and in Section 6.4.
Duration of Study (Clinical Stage)	The duration for an individual subject is approximately 13 months.
Number of Subjects	Up to 84
Inclusion Criteria	1. Healthy males and females between 20 and 40 (inclusive) years of age. 2. Subjects who provide written informed consent to participate in the study. 3. Subjects in general good health in the opinion of the investigator as determined by medical history, vital signs and a physical examination. 4. No clinically significant abnormalities in hematology, blood chemistry, or urinalysis lab tests at screening. 5. Women of child-bearing potential must practice an acceptable method of birth control or practice abstinence during the study period or be surgically sterilized, from screening visit throughout the treatment phase and for 28 days after the last injection and agree to undergo repeated pregnancy tests. 6. Subjects must be able to understand the requirements of the study and must be willing to comply with the requirements of the study.
Exclusion Criteria	1. Known history of significant medical disorder, which in the investigator's judgment contraindicates administration of the vaccine or may interfere with the subject's compliance or the interpretation of study assessment parameters.

	2. Any clinically significant abnormality upon physical examination or in the clinical laboratory tests at screening visit. 3. Treatment with immune suppressive agents. 4. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose. 5. History of HBV infection or confirmed exposure to hepatitis B virus. 6. Previous vaccination against Hepatitis B. 7. Positive for HBsAg, anti-HBsAg antibodies, anti-HBc antibodies, anti-HCV antibodies or anti- HIV antibodies. 8. Drug abusers 9. Known hypersensitivity or allergy to any component of the study vaccine. 10. BMI < 18.5 or ≥ 30 Kg/m^2. 11. Known concomitant disease or any other medical condition that is considered by the investigator likely to interfere with the subject's compliance or the interpretation of study assessments. 12. Any acute illness (e.g. acute infection) within 48 hours prior to the first study drug administration that is considered of significance by the Principal Investigator. 13. Female subjects: pregnant, lactating or planning a pregnancy. 14. Any confirmed or suspected immunosuppressive or immunodeficient condition. 15. Receipt of blood or immunoglobulin transfusion six months prior to the first vaccine dose and during the course of the trial. 16. Unwilling or unable (in the judgment of the investigator) to comply with all the requirements of the protocol. 17. Participate in another clinical trial within 3 months prior to first vaccination (calculated from the previous study's last dosing date).
Safety Assessments	The primary safety endpoint is the frequency, severity, and duration of adverse events (AEs), including clinically significant laboratory abnormalities after administration of Sci-B-Vac™. Safety will be evaluated on the basis of the following assessments: • AEs: continuous (starting from informed consent signature until end of study) • Recording of concomitant medications: continuous (starting from informed consent signature until end of study) • Physical examination: on screening and on study termination visit. • 12-lead ECG: on screening and on study termination visit. • Vital signs (sitting BP, HR, RR, oral temperature): on screening, on each treatment (vaccination) visit within 60 minutes before vaccine administration, at 60 (± 15) minutes after vaccination and on study termination visit.

	• Safety laboratory evaluations (blood and urine): On screening, before each vaccine administration and on study termination visit. Safety laboratory variables are outlined in Appendix B.
Statistical Methodology	A total of 84 subjects, are expected to be recruited into study. The trial will follow-up eligible subject for a total duration of 12 months. One interim analysis is planned to be conducted at the time when approximately 50% of the subjects will reach Month 7 or early terminated the study. **Interim and Final Analyses** One interim analysis is planned for possible early termination of the study. The interim analysis will be performed at the time when approximately 50% of the subjects will reach Month 7 (1 month after the 3rd vaccine) or early terminated the study. **Significance Level** The overall significance level for this study will be 5% using two-tailed tests. **Sample Size Rationale**: Sample size determination was performed under the following assumptions: • The primary endpoint for the study is the Seroprotection Rate (SPR), defined as the proportion of subjects with anti-HBs antibody titer at least equal to 10mIU/ml, at Month 7 (i.e. one month after the third immunization with Sci–B-Vac™). Subjects early terminated from the study for any reason at any time while having an anti-HBs antibody concentrations ≥ 10mIU/ml will be considered among those who met endpoint. • It is expected that the true rate of SPR following treatment with Sci–B-Vac™ is 95% or more. • The principal analysis of the primary endpoint will be a non-inferiority analysis testing the below hypothesis: • H_0: P-p_0 <= -Margin • H_1: P-p_0 > -Margin • Where p_0, the assumed true SPR is 95% and the non-inferiority margin is 9.0%, employing that study will be considered successful if the lower bound of the 95.0% exact CI will be 86.0% or more (lower non-inferiority limit). • The rational for sample size calculation is based on demonstrating an expected SPR rate of 95%. The lower bound of a calculated 95% confidence interval (CI) using Exact binomial method ensures that the actual SPR rate will not exceed the calculated lower limit (will not be lower than the lower bound). • The sample size is adjusted to a total of 84 subjects to account for an anticipated withdrawal rate of approximately 20%.

	Sample Size Justification: When the sample size is 70, a one-sided 95.0% confidence interval (CI) for a single proportion using Exact binomial method will demonstrate a lower bound of 86.0% or more for an expected proportion of 0.95. **Primary Endpoint Definition:** The primary endpoint of the study is the Seroprotection rate (SPR), defined as the proportion of subjects with anti-HBs antibody titer at least equal to 10mIU/ml, at Month 7 (i.e. one month after the third immunization with Sci–B-Vac™). Subjects early terminated from the study for any reason at any time while having an anti-HBs antibody concentrations ≥ 10mIU/ml will be considered among those who met endpoint. **Principal Analysis of the Primary Endpoint:** The principal analysis of the primary endpoint will employ a non-inferiority analysis [SAS PROC FREQ with binomial (noninf margin=0.09 p=(1-α) exact)] statement will be used for testing the below hypothesis: H_0: P-p_0 <= -Margin H_1: P-p_0 > -Margin Where p_0, the assumed true SPR is 95% and the non-inferiority margin is 9.0%, employing that study will be considered successful if the lower bound of the (1-α) exact CI will be 86.0% or more.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
AE	Adverse Events
ANA	Antinuclear antibodies
ALT	Alanine transaminase
Anti-HBc	Antibodies to hepatitis B core antigen
Anti-HBs	Antibodies to HBsAg
Anti-HCV	Antibodies to hepatitis C virus
AST	Aspartate aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
cm	Centimeter
CRC	Clinical Research Center
CRF	Case Report Form
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMR	Geometric mean ratio
GSK	Glaxo Smith Kline
h	Hours
HBsAg	Hepatitis B Surface Antigen
HIV	Human immunodeficiency virus
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
IMP	Investigational Medicinal Product
IP	Investigational Product
IRB	Institutional Review Board
IRB	Institutional Review Board
Kg	Kilogram
m	Meter
mg	Milligram

Abbreviation/Term	Definition
min	Minute
mITT	Modified intention-to-treat analysis
ml	Milliliter
MOH	Ministry of Health
MSD	Merck Sharp and Dome
N/A	Not Applicable
ºC	Degrees centigrade
OTC	Over the Counter
OTC	Over the counter
PI	Principal Investigator
PQC	Product Quality Complaint
PT	Prothrombin Time
PT/INR	Prothrombin time/International Normalized Ratio (for blood clotting time)
QA	Quality Assurance
R&D	Research and Development
RBC	Red blood cells
RBC	Red blood cell
RDW	RBC distribution width
RR	Respiration rate
SAE	Serious Adverse Event
SOP	Standard Operation Procedures
SPR	Seroprotection rate
SUSAR	Suspected unexpected serious adverse reaction
TASMC	Tel Aviv Sourasky Medical Center
TEAE	Treatment emergent adverse events
WBC	White blood cell
WHO	World Health Organization
µg	Microgram

1 INTRODUCTION

1.1 BACKGROUND – HEPATITIS B VIRUS INFECTION

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus. It can cause chronic liver disease and chronic infection and puts people at high risk of death from cirrhosis of the liver and liver cancer. More than 240 million people have chronic (long-term) liver infections. More than 780 000 people die every year due to the acute or chronic consequences of hepatitis B.

In highly endemic areas, HBV is most commonly spread from mother to child at birth, or from person to person in early childhood. Perinatal or early childhood transmission may also account for more than one third of chronic infections in areas of low endemicity, although in those settings, sexual transmission and the use of contaminated needles are the major routes of infection.

High risk groups include: people who frequently require blood or blood products, dialysis patients, recipients of solid organ transplantations, people interned in prisons, injecting drug users, household and sexual contacts of people with chronic HBV infection, people with multiple sexual partners, as well as health-care workers and others who may be exposed to blood and blood products through their work and travelers who have not completed their hepatitis B vaccination series.

The hepatitis B virus can survive outside the body for at least 7 days. During this time, the virus can still cause infection if it enters the body of a person who is not protected by the vaccine.

Most people do not experience any symptoms during the acute infection phase. However, some people have acute illness with symptoms that last several weeks, including yellowing of the skin and eyes (jaundice), dark urine, extreme fatigue, nausea, vomiting and abdominal pain. In some people, the hepatitis B virus can also cause a chronic liver infection that can later develop into cirrhosis of the liver or liver cancer*.

Five to ten percent of infected adults are unable to eliminate the virus following acute infection, and develop persistent viral infection which lasts more than 6 months; this is designated as a hepatitis B surface antigen (HBsAg) carrier state. It has been estimated that there are >200 million HBsAg carriers worldwide [1].

The first generation, plasma-derived hepatitis B vaccines were developed in the US and France in the late 1970s. In the mid 1980s, second generation recombinant DNA hepatitis B vaccines were constructed in yeasts transfected with HBV-DNA sequences coding for the small HBV envelope protein. These vaccines have gradually replaced the first generation plasma derived vaccines and are currently used for universal vaccination of newborns and adults at risk in >170 countries worldwide. Third generation HBV vaccines containing one or two additional HBV envelope proteins (Pre-S1 and Pre-S2) have been developed in Germany, France and Israel in transfected mammalian cells (Chinese Hamster Ovarian cells). These vaccines have in general an enhanced efficacy as compared to yeast derived vaccines [2,3,4]

1.2 SCI-B-VAC™ PRODUCT DESCRIPTION

Sci-B-Vac™ is a recombinant hepatitis B vaccine, manufactured by SciVac Israel Ltd. It is produced in mammalian Chinese hamster ovary (CHO) cells, transfected with appropriate sequences that code for the HBV envelope proteins SHBs-S, MHBs-pre-S_2, and LHBs-pre-S_1. The gene coding for these antigens, including the native HBs promoter, enhancer, and poly a signal, was

*World health organization, Hepatitis B, Fact sheet N°204 Updated July 2014

cloned into a plasmid vector containing the mouse dihydrofolate reductase (DHFR) expression cassette. The plasmid was used to establish the producer CHO cell line. Transfected cells were selected for $DHFR^+$ phenotype, and gene co-amplification was done with methotrexate. The immunogenicity of the pre-S_2 and pre-S_1 antigens in the final vaccine preparation was demonstrated in BALB/c mice and rabbits, as well as in babies who developed appropriate anti-pre-S1 and anti-pre-S2 antibodies following immunization with Sci-B-Vac™ [5,6,7]. The physical properties of the HBV envelope particles produced in CHO cells and the immune response to HBV nucleocapsid and Pre-S/S envelope proteins have been characterized[5,8-13].

Sci-B-Vac™ is approved by Health Authorities for marketing in 13 countries including Israel, Central Africa, Ivory Coast, Georgia, Gabon, Guinea Equtorial, Hong Kong, Moldova, Niger, Nigeria, Philippines, Senegal and Vietnam.

Since 2005, more than 1.5 million units of Sci-B-Vac™ have been sold in Israel for vaccination against Hepatitis B in babies, children and adults.

1.3 SUMMARY OF CLINICAL STUDIES

To date, thirteen open label clinical studies (plus three extensions) and 4 single blinded clinical studies utilizing Sci-B-Vac™ (also distributed under the trade names Bio-Hep B and Hepimmune) have been completed[16-28].

The clinical development of Sci-B-Vac™ included: two phase I studies in adults [16,17], three phase II dose-range studies in adults [16-18] one in children [19] and four in neonates [20-23], two phase II and one phase III comparative studies in adults [24-26], one Phase II study in children[27] and one Phase II study in neonates[28]. Three of the studies (one in adults and two in children) were extended in order to increase the size of the group vaccinated with Sci-B-Vac™. In the adult phase I studies, subjects received 10 µg of Sci-B-Vac™. Sci-B-Vac™ was given once to prime the immune memory; the first dose was followed by two booster doses at 1 and 6 months after primary immunization[16]. This immunization schedule is set by convention. In the first adult Phase II study in Singapore[16], subjects were randomized to receive 5 µg or 10 µg of Sci-B-Vac™ in three injections. Once tolerability/safety and dose-dependent efficacy were demonstrated, the clinical development of two more adult dose-range studies were performed in Thailand and Israel [17,18,]followed by a dose-range study performed in Poland with children[19] and four neonate studies in Poland, Singapore and Vietnam[20-23]. After seroconversion rates and the efficacy/dose relationship were more firmly established, five comparative studies which assessed the efficacy of Sci-B-Vac™ relative to that of conventional yeast derived vaccines were performed in adults, children and neonates[24-28].

From the early phase II studies it became evident that a significant number of vaccinees develop high anti-HBs titers following vaccination. In study HBN014-01[23], conducted in Vietnam, a dose-response relationship could be demonstrated. More vaccinees who received the 5 µg dose/injection had anti-HBs titers ranging from 1001-10,000 mIU/ml as compared to those who received the 2.5 µg dose/injection. More than 60% of the vaccinees in the 5 µg dose group developed these high titers within three months after the third vaccination. At the end of the study 95.6% (196/205) of the subjects were seroprotected.

The high efficacy of Sci-B-Vac™ was further confirmed in adults[25,26] and in neonates[28]. In these comparative controlled studies conducted in Israel, more than 50% of adult vaccinees who received the 10 µg/dose and neonates who received the 2.5 µg dose had anti-HBs titers above 10,000 mIU/ml after the third vaccination. These percentages were greater than those observed in vaccinees who received the yeast-derived vaccines. Furthermore, no non-responders were observed in

immunized neonates who received 2.5 µg Sci-B-Vac™. In adults, the number of non-responders who received Sci-B-Vac™ was very small (3.5%, 18/513) as compared to vaccinees immunized with Engerix-B® (13.7%, 43/415).

1.4 STUDY RATIONALE

Each Sci-B-Vac™ lot released to the market is tested in comparison to a reference batch, which has to be tested in a human clinical trial. Therefore, SciVac Ltd. is conducting this study to evaluate the efficacy of a Sci-B-Vac™ batch in support of its qualification as new reference standard. In accordance with the European Pharmacopeia (Ph.Eur. 1056), this reference standard is to elicited at least 95% seroprotection in young, healthy subjects.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To validate the new in-house reference standard vaccine for routine quality control purposes, in compliance with the European Pharmacopeia and the Israeli Ministry of Health.

2.2 SECONDARY OBJECTIVES

1. To characterize the immunological response throughout the study.
2. To monitor the subjects for safety throughout the study period

2.3 EXPLORATORY OBJECTIVES

1. To collect blood samples for the *in vitro* validation of anti-HBs, anti-preS1 and anti-preS2 antibodies assays.
2. To assess the anti-preS1 and anti-preS2 antibodies responses upon vaccination.
3. To investigate additional protective mechanisms of action and the type of immune response triggered by the vaccination. No genetic tests will be performed.

3 STUDY ENDPOINTS

3.1 PRIMARY ENDPOINT

Seroprotection rate (SPR), defined as the proportion of subjects with anti-HBs antibody titer at least equal to 10mIU/ml, at Month 7 (i.e. one month after the third immunization with Sci-B-Vac™). Subjects early terminated from the study for any reason at any time while having an anti-HBs antibody concentrations ≥ 10mIU/ml will be considered among those who met endpoint.

3.2 SECONDARY ENDPOINTS

1. SPR one month after the first injection and at every month until Month 6 inclusive and at months 9 and 12.
2. Percentage of subjects with anti-HBs antibodies titer ≥ 100mIU/ml at Month 0, and then at every month until Month 7 inclusive and at months 9 and 12.

3. The geometric mean concentration (GMC) as determined by anti-HBsAg antibody titers at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.

3.3 EXPLORATORY ENDPOINTS

1. The anti-preS1 antibody titers measured at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.
2. The anti-preS2 antibody titers measured at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.

4 STUDY DESIGN

4.1 OVERALL STUDY DESIGN

This will be a post-marketing, open-label, single arm study in healthy volunteers who had never been vaccinated with any hepatitis B vaccine and who are HBs antigen, anti-HBc and anti-HBsAg antibodies seronegative.

The study assessments will be performed as described in the study flow chart (See Appendix A).

This study will consist of three periods:

Screening Period (Visit 1: up to 1 month prior to first vaccination)

After signing of the informed consent form (ICF), screening procedures will be carried out as specified in Section 6.1.1 and Appendix A.

Treatment and Follow-up Period (Visits 2-8: Months 0-6)

Subject identification number will be assigned to all eligible subjects following assessment of inclusion and exclusion criteria.

All eligible subjects will receive Sci-B-Vac™ vaccine. The treatment phase will include three I.M. doses of Sci-B-Vac™ administered in the deltoid muscle on Month 0, Month 1, and Month 6. Subjects will be followed up for safety evaluations and for efficacy (by anti-HBs, anti-pre-S1 and anti-pre-S2 testing), every month. The previous injection site will be inspected before the second and third administration.

The following assessments will be performed during each treatment visit: recording of AEs and concomitant medications, vital signs and blood tests for quantitative anti-HBs, anti-preS1 and anti-preS2 antibodies and safety assessment (including blood and urine laboratory tests). Female subjects will also undergo a urine pregnancy before each injection. Vital signs are not required on follow-up visits when vaccine is not administered.

Post-Vaccination Follow-up Period (Visits 9-11: Months 7, 9 and 12)

Additional subject follow- up visits will take place 1, 3 and 6 months after the last vaccine administration. On each visit, subjects will be inquired about AEs and concomitant medications, and blood samples for quantitative anti-HBs, anti-preS1 and anti-preS2 antibodies levels will be drawn. The last visit (Month 12) is a study termination visit in which all subjects will also undergo physical examination, laboratory safety assessments (CBC, blood chemistry and urinalysis), vital

signs measurement and a 12-lead ECG. In addition, female subjects will undergo a urine pregnancy test.

5 SELECTION OF STUDY POPULATION

5.1 NUMBER OF SUBJECTS

Up to eighty four (84) healthy subjects will be enrolled in the study

5.2 INCLUSION CRITERIA

1. Healthy males and females between 20 and 40 (inclusive) years of age.
2. Subjects who provide written informed consent to participate in the study.
3. Subjects in general good health in the opinion of the investigator as determined by medical history, vital signs and a physical examination.
4. No clinically significant abnormalities in hematology, blood chemistry, or urinalysis lab tests at screening.
5. Women of child-bearing potential must practice an acceptable method of birth control (as specified in Section 8.2) or practice abstinence during the study period or be surgically sterilized, from screening visit throughout the treatment phase and for 28 days after the last injection and agree to undergo repeated pregnancy tests.
6. Subjects must be able to understand the requirements of the study and must be willing to comply with the requirements of the study.

5.3 EXCLUSION CRITERIA

1. Known history of significant medical disorder, which in the investigator's judgment contraindicates administration of the vaccine or may interfere with the subject's compliance or the interpretation of study assessment parameters.
2. Any clinically significant abnormality upon physical examination or in the clinical laboratory tests at screening visit.
3. Treatment with immune suppressive agents.
4. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose.
5. History of HBV infection or confirmed exposure to hepatitis B virus.
6. Previous vaccination against Hepatitis B.
7. Positive for HBsAg, anti-HBsAg antibodies, anti-HBc antibodies, anti-HCV antibodies or anti- HIV antibodies.
8. Drug abusers
9. Known hypersensitivity or allergy to any component of the study vaccine.
10. BMI < 18.5 or ≥ 30 Kg/m^2.
11. Known concomitant disease or any other medical condition that is considered by the investigator likely to interfere with the subject's compliance or the interpretation of study assessments.

12. Any acute illness (e.g. acute infection) within 48 hours prior to the first study drug administration that is considered of significance by the Principal Investigator.
13. Female subjects: pregnant, lactating or planning a pregnancy.
14. Any confirmed or suspected immunosuppressive or immunodeficient condition.
15. Receipt of blood or immunoglobulin transfusion six months prior to the first vaccine dose and during the course of the trial.
16. Unwilling or unable (in the judgment of the investigator) to comply with all the requirements of the protocol.
17. Participate in another clinical trial within 3 months prior to first vaccination (calculated from the previous study's last dosing date).

5.4 SUBJECT IDENTIFICATION

Each subject who signed the informed consent will be identified by a unique CRC internal identification number and a screening number that will be a unique identifier of the subject through the study. The screening number will include the letter "S", the site number and a sequential chronological order per site of three digits.
Subjects who are dosed will be assigned a recruitment number which will include the letter "R", the site number and a sequential chronological order per site of three digits.

5.5 SCREENING FAILURES

Subjects who fail to meet the entrance criteria at any stage during the screening period are defined as screen failures. All screen failures will be documented on the screening log, which documents the screening number, subject's initials and reason(s) for screen failure. The screening log will be kept in the Investigators Site File.

Screen failure subjects will be withdrawn from the study and will not count towards the total enrolled or total eligible subjects.

5.6 REMOVAL, REPLACEMENT, OR EARLY WITHDRAWAL OF SUBJECTS FROM TREATMENT OR ASSESSMENT

Subjects are free to discontinue their participation in the study at any time and without prejudice to further treatment. The Investigator must withdraw any subject from the study if that subject requests to be withdrawn, or if the subject present positive serological marker of hepatitis B infection, or it is determined that continuing in the study would result in a significant safety risk to the subject.

Subjects discontinued or withdrawn from the study will **not** be replaced after first dosing. If insufficient number of subjects are expected to complete the study, recruitment of additional volunteers will be considered. Approval by the IRB will be required.

The subject's participation in this study may be discontinued due to the following reasons:

- Positive serological marker for hepatitis B infection
- Request of regulatory agency, or Sponsor or Principal Investigator
- Subject withdrew consent
- Adverse event (AE)
- Subject is unwilling or unable to continue the study or is lost-to-follow-up

- Subject is non-compliant with study procedures/study protocol
- Investigator decides that withdrawal from the study is in the best interest of the subject
- Subject needs medication not allowed in the protocol
- Any clinically significant change in subject's medical condition.

5.7 HANDLING OF WITHDRAWALS

If a subject is withdrawn from the study or fails to return either at his/her request or at the Investigator's discretion, every effort should be made to determine the reason. This information will be recorded on the subject's case report form (CRF). All subjects who withdraw from the study prematurely, regardless of cause, should undergo all study termination assessments (see Section 6.1.11). It is crucial to obtain follow-up data for any subject withdrawn because of an AE or abnormal laboratory test finding. In any case, every effort must be made to undertake safety follow-up procedures.

If withdrawal is caused by a Suspected Unexpected Serious Adverse Reaction (SUSAR), it will be reported to the institutional review board/independent ethics committee (IRB/IEC) and Sponsor.

5.8 TERMINATION OF STUDY BY SPONSOR

The Sponsor reserves the right to discontinue the study at any time for any reason. Such reasons may be any of, but not limited to, the following:

- Occurrence of AEs unknown to date in respect of their nature, severity, and duration or the unexpected incidence of known AEs
- Medical or ethical reasons affecting the continued performance of the study

Regulatory Authorities also have the right to terminate the study for any reason.

5.9 TERMINATION OF STUDY

A subject will be considered to have completed the study if he or she has completed all assessments at Month 12 of the study.

6 STUDY PROCEDURES AND SCHEDULES

The schedule of activities for this study is shown in Appendix A. No protocol-related procedures should be performed before subjects provide written informed consent. Study related events and activities including specific instructions, procedures, concomitant medications, dispensing of study drugs, and descriptions of AEs should be recorded in the appropriate source documents and CRF.

6.1 VISIT SCHEDULES

6.1.1 Visit 1 - Screening (within 4 weeks before Visit 2)

Subjects will sign an informed consent form and will be assessed for their eligibility to participate in the study.

The following screening assessments will be performed at pre-study for each subject:

- Medical history (including concomitant medications)
- Demographics (gender, date of birth)
- Vital signs: blood pressure and heart rate - sitting, respiration rate (RR), oral body temperature
- Height
- Weight
- BMI (calculated as kg/m^2)
- Physical examination
- 12-lead ECG
- Laboratory safety screens as outlined in Appendix B
- For female subjects serum βHCG
- Serology tests as outlined in Appendix A
- Compliance with inclusion/exclusion criteria

The amount of blood drawn in this visit is approximately 26 ml.

6.1.2 Visit 2 - First Vaccine Administration: Month-0 (Day 1)

Dosing day will be designated "**Month 0, Day 1**".

The subjects will be admitted to the CRC in the morning of treatment. They will be interviewed by the CRC study personnel regarding change in concomitant medications or changes to their health status since the Screening visit. Female subjects will undergo a urine pregnancy test, and eligibility of inclusion/exclusion criteria will be reviewed.

Prior to dosing (within 60 min before vaccination), the following activities will be completed:

- Vital signs, measured following 3 min rest (sitting BP, HR, RR and oral temperature);
- A blood sample for serology, safety laboratory testing and for further investigational purposes (55 ml) will be drawn.
- Urine sample will be collected for safety testing.

Vaccine administration: Each subject will receive the injection as described in Section 7.3. The time, date of vaccination and side of injection (i.e. left or right arm) will be documented in the CRFs and on the CRC Drug Administration Records.

After vaccination: Subjects remain in the CRC for approximately 1 hour after injection. Vital signs (sitting BP, HR, respiratory rate, and oral body temperature) will be measured at 60 (± 15) minutes after treatment, and recorded as appropriate.

Before discharge from the CRC a study physician will examine the injection site using a grading score (Appendix C).

The subjects will then be released from the CRC following a study physician's approval.

6.1.3 Visit 3 - Second Vaccine Administration: Month 1, (Week 4± 3 days)

The second vaccination will take place 28 (±3) days after the first vaccination (Visit 2). The previous injection site will be inspected before the second administration. Procedures will be identical to Visit 2,. except the volume of blood drawn for serology, safety laboratory testing and for further investigational purposes, which will be lower (40 ml).

6.1.4 Visit 4 – Follow-up: Month 2 (Week 8± 3 days)

Subjects will arrive in the CRC and will be will be interviewed by the CRC study personnel regarding change in concomitant medications or changes to their health status since the last visit. Blood samples for serology and for exploratory purposes (35 mL) will be drawn and the subject will be released from the CRC.

6.1.5 Visit 5 – Follow-up: Month 3 (Week 12± 3 days)

Procedures will be identical to Visit 4.

6.1.6 Visit 6 – Follow-up: Month 4 (Week 16± 3 days)

Procedures will be identical to Visit 4.

6.1.7 Visit 7 – Follow-up: Month 5 (Week 20± 3 days)

Procedures will be identical to Visit 4.

6.1.8 Visit 8 - Third Vaccine Administration: Month 6, (Week 24± 3 days)

The third (last) vaccination will take place 5 months after the second vaccination (Visit 3). The previous injection site will be inspected before the third administration. Procedures will be identical to Visit 2, except the volume of blood drawn for serology, safety laboratory testing and for further investigational purposes, which will be lower (35 ml).

6.1.9 Visit 9 – Follow-up: Month 7 (Week 28± 3 days)

Subjects will arrive in the CRC and will be will be interviewed by the CRC study personnel regarding change in concomitant medications or changes to their health status since the last visit. Blood samples (50 ml) for serology and for further investigational purposes will be drawn and the subject will be released from the CRC.

6.1.10 Visit 10 – Follow-up: Month 9 (Week 36± 8 days)

Procedures will be identical to Visit 9.

6.1.11 Visit 11 – Study Termination: Month 12 (Week 48± 8 days)

The following assessments will be performed:

- Physical examination
- Vital signs: (sitting BP, HR, RR, oral temperature)
- 12-lead ECG
- Laboratory safety tests (See Appendix B)
- Serology tests

- Blood samples for additional investigational purposes
- AE and concomitant medication recording

The amount of blood drawn in this visit is approximately 28 ml

The total amount of blood drawn for serology and routine safety laboratory tests will be about 424 ml over a period of 13 months.

6.2 UNSCHEDULED VISIT

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the Investigator due to medical considerations. The date and reason for the unscheduled visit will be recorded. AE monitoring and concomitant medication recording will be performed by the Investigator. Other procedures and evaluations will be completed as deemed necessary by the Investigator and may include (but not limited to) safety laboratory tests, ECG, vital signs and physical examination.

6.3 BLOOD SAMPLING FOR IMMUNOGENICITY

6.3.1 Serology Tests

The immunogenicity of the vaccine will be assessed by the anti-HBsAg, anti-preS1 and anti-preS2 antibody levels at each visit, from visit 2 till visit 11, as presented in Appendix A.

6.3.2 Blood Sampling and Processing.

Processing and storage of the samples are detailed in the lab manual provided by the Sponsor.

6.3.3 Shipment of Samples to the Bioanalytical Laboratory

Samples will be shipped in a cold pack to the central laboratory on the same day it is drawn from the subject, as detailed in the lab manual provided by the Sponsor.

6.4 SAFETY ASSESSMENTS

Safety assessments will be based on AEs reported by the subject or observed by the Investigator, concomitant medication use, clinically significant changes from baseline of vital signs, ECG, physical examination, and safety laboratory tests (hematology, chemistry, and urinalysis).

6.4.1 Adverse Events (AEs)

AEs will be recorded continuously starting from the signing of the ICF through the Study Termination visit, in those subjects who have been actually dosed.

AEs reported prior to dosing will be recorded in the CRF and considered non-treatment emergent AEs. Any new systemic effect that occurs between scheduled visits should be brought to the attention of the Investigator and recorded in the subject's medical file and in the CRF.

The systemic symptoms will be graded according to the FDA Guidance to Industry[29] (see grading scale in Appendix C Table 3).

6.4.2 Local reaction at injection site

Local reaction at injection site, based on the FDA Guidance to Industry[29] (see grading scale in Appendix C Table 1) will be assessed by a study physician on treatment visits.

6.4.3 Vital Signs

Vital signs (sitting systolic and diastolic blood pressure, heart rate, respiratory rate and oral temperature) will be measured after at least 3 minutes rest as per standard practice at the investigational site at the following time points:

- On screening,
- On each treatment visits (Visits 2, 3 and 8): within 60 minutes before vaccination, 60 (± 15) minutes after vaccination.
- On Study Termination visit

Changes in vital signs determined by the Investigator to be clinically significant will be noted as an AE on the appropriate CRF and in the subject's file. Such abnormalities will be closely monitored until stabilized or resolved.

Vital Signs will be graded according to the FDA Guidance to Industry[29] (see grading scale in Appendix C Table 2).

6.4.4 Electrocardiogram (ECG)

A 12-lead ECG will be performed at the following time points:

- On screening,
- On Study Termination visit

6.4.5 Physical Examination

Complete physical examination will be performed at the following time points:

- On screening,
- On Study Termination visit

Significant changes from baseline examination on screening will be recorded as AEs in the CRF and in the subject's file.

6.4.6 Safety Laboratory Tests

Safety laboratory tests including biochemistry, hematology and urinalysis (see details in Appendix B) will be performed at the following times:

- On screening;
- On each treatment visits (Visits 2, 3 and 8): within 60 minutes before vaccination
- On Study Termination visit (without the screening serology tests)

All safety (chemistry, hematology urinalysis, serology and urine tests will be carried out by AML Laboratories, except urine test for pregnancy which will be performed at the trial site by the CRC staff.

Clinically significant laboratory tests or tests of unknown significance which are outside the normal range may be repeated as clinically indicated until the values return to normal, or until the etiology has been determined and the condition considered stable. Abnormal laboratory test results that are considered to be clinically significant by the investigator will be reported as an AE in the CRF.

7 INVESTIGATIONAL PRODUCT

7.1 DESCRIPTION OF INVESTIGATIONAL PRODUCT

Sci-B-Vac™ is a recombinant Hepatitis B vaccine, produced by SciVac Israel Ltd. It contains the 3 surface antigens of the HBV: HBs, preS1 and preS2 antigens. Each 1ml dose contains sterile 10µg HBs antigen. It is formulated for intramuscular injection supplied in a single use vials containing 1 ml suspension. The components of the investigational vaccine are produced under aseptic conditions and according to the rules of current Good Manufacturing Practice and guidelines applicable to IMPs (investigational medicinal products). The vaccine lot used in this trial will be tested and released by the Quality Assurance Department of the Sponsor.

7.2 PACKAGING AND LABELLING OF INVESTIGATIONAL PRODUCT

All clinical supplies will be provided from the designated commercial batch packed and labeled in compliance with the Good Manufacturing Practices of drugs used in clinical trials and with the Israeli Ministry of Health Guidelines for Clinical Trials in Human Subjects. All study vaccines provided will be appropriately documented.

7.3 STUDY DRUG ADMINISTRATION

7.3.1 Vaccination Regimen:

One ml of a single Sci-B-Vac™ Vaccine vial (i.e. 10 µg) will be administered intramuscularly in the deltoid area of the arm, on Month 0, 1 and 6, according to common immunization practice.

7.3.2 Preparation of the Vaccine.

Prepare vaccine just prior to administration. Agitate the vial to mix the vaccine thoroughly and obtain a uniform suspension prior to withdrawing each dose. Whenever solution and container permit, inspect the vaccine visually for discoloration, precipitation or if it cannot be re-suspended prior to administration. If problems are noted (e.g., vaccine cannot be re-suspended), the vaccine should not be administered.

A separate vial should be used for each subject.

7.3.3 Administration of the Vaccine.

The vaccine should be administered while wearing gloves. Once loaded into the syringe with a 22–25 gauge needle, the vaccine should be administered to the subjects immediately.

Vaccine administration information including date, time and side of the injection (i.e. left or right arm) will be documented in the Case Report Forms and on the Drug Administration Records.

7.4 SHIPMENT OF INVESTIGATIONAL PRODUCT

Prior to study start, study medications will be supplied to the CRC by the Sponsor. It is the responsibility of the Sponsor to ensure the vaccine is kept at 2-8°C during the shipment.

The Sponsor must notify the Investigator/study staff prior to dispatch of drug supplies, with the anticipated date of their arrival, addressed to:

Clinical Trials Unit
TASMC Pharmacy
Tel-Aviv Sourasky Medical Center
6 Weizmann Street,
Tel-Aviv 64239, Israel

Shipment of study drug supplies for the study will be accompanied by a shipment form describing the contents of the shipment drug information, acknowledgement of receipt and other appropriate documentation. The shipment form will assist in maintaining current and accurate inventory records.

7.5 RECEIPT AND STORAGE OF INVESTIGATIONAL PRODUCT

All study supplies should arrive at the Pharmacy in sufficient quantity and in time to enable dosing as scheduled.

The investigational product will be accompanied by a shipment form and appropriate documentation.

Vaccines will be stored at the hospital pharmacy in an appropriate locked room until dosing, refrigerated at an average temperature between 2ºC to 8ºC. During the storage at the pharmacy, the temperature of the refrigerator will be monitored continuously and recorded by a pharmacist or another member of study staff who will record refrigerator temperature log. The Sponsor should be notified for any deviation from the storage conditions. Vaccine vials should never be exposed to freezing temperatures.

The Investigator will issue a prescription, and the vaccines will be picked up from the pharmacy before administration. The time at which the vaccine exits the pharmacy will be recorded. The vaccines will be transferred from the pharmacy to the CRC in a closed icebox without ice, according to the Sponsor's instructions, and time limitation until vaccine administration will be provided based on stability prior to first dosing. The icebox will be provided by the Sponsor

7.6 ACCOUNTABILITY OF INVESTIGATIONAL PRODUCT

The TASMC pharmacy will be responsible for recording the receipt of all drug supplies and for ensuring the supervision of the storage and allocation of these supplies. When a shipment is received, the pharmacist verifies the quantities received and the accompanying documentation and returns the acknowledgment of receipt to the Sponsor.

Drug administration will be recorded in the source documents, in the CRFs and in the Drug Administration Record form. The latter includes the subject identification, quantity (volume) and

date of administration. The containers from which the drug was administered to the subjects will be retained for dose confirmation.

At the end of the study, delivery records of study drug will be reconciled with used / unused stocks and appropriate forms will be filled in, to verify that all used, unused or partially used supplies have been returned and that no study supplies remain in the Investigator's possession.

All unused drug supplies, partially used and empty containers will be returned to the Sponsor or disposed of according to the Sponsor's instructions.

8 STUDY RESTRICTIONS

8.1 CONCOMITANT MEDICATIONS

The following medications are prohibited for use by the subject throughout the study:

- Systemic corticosteroid treatment less than 14 days before first vaccination and throughout the study.
- Immunosuppressant medications (e.g. mycofenolate mofetil, cyclosporine, cyclophosphamide etc.)
- Biological immune-modifying agents (e.g. anti TNF alfa, anti CD20)

8.2 ADDITIONAL RESTRICTIONS

Women of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-HCG) test on screening (and negative consecutive urine tests during the study) and be willing and able to use an acceptable method of birth control (acceptable methods of birth control include: intrauterine devices, oral contraceptive, contraceptive patch, long-acting injectable contraceptive or double-barrier method - condom or diaphragm with spermicide) from the screening visit through the EOS visit, or declare that they are abstaining from sexual intercourse, or be surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or post-menopausal.

9 SAFETY AND PHARMACOVIGILANCE

9.1 ADVERSE EVENT DEFINITION

An AE is defined as "Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related".

An AE (also referred to as an adverse experience) can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality or seriousness. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

An abnormal result of diagnostic procedures including abnormal laboratory findings will be considered an AE if it fulfills one or more of the following:

- Results in subject's withdrawal by the Investigator
- Is associated with a serious adverse event (SAE)
- Is associated with clinical signs or symptoms
- Is considered by the physician to be of clinical significance (a laboratory abnormality that is not clinically significant will not be considered an AE)

A new condition or the worsening of a pre-existing condition will be considered an AE.

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Suspected adverse reaction is “any adverse event for which there is a reasonable possibility that the drug caused the adverse event.”

AEs do not include the following:

- Stable or intermittent chronic conditions (such as myopia requiring eyeglasses) that are present prior to study entry and recorded in the subject's file and do not worsen during the study
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if not present at baseline
- Overdose of either study drug or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred)
- Pregnancy alone is not considered an AE. Elective abortions without complications should not be handled as AEs.

All AEs, whether observed by the Investigator or designee or volunteered by or elicited from the subject, should be recorded individually in the CRF. AEs will be recorded from the time a subject has signed the ICF and throughout the study, including the follow up period, in those subjects who have been dosed at least once.

Severity of the AE will be assessed by the investigating physician in accordance with the definitions in Appendix C. An SAE must fulfill the requirements listed in the Section 9.2.

The Investigator will document in his/her opinion the relationship of the AE to the study drug using the criteria outlined in definition of adverse events relationship to study drug (Table 1).

Table 1: Definition of adverse events relationship to study drug

TERM	DEFINITION	CLARIFICATION
Unrelated	In general, this category can be considered applicable to those adverse events, which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug.	An adverse experience may be considered unlikely related if or when (must have two): • It does not follow a reasonable temporal sequence from the administration of the test drug. • It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • It does not follow a known pattern of response to the test drug. • It does not reappear or worsen when the drug is re-administered.
Possibly Related	This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration appears unlikely but cannot be ruled out with certainty.	An adverse experience may be considered possibly related if or when (at least two of the following): • It follows a reasonable temporal sequence from administration of the drug. • It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • It follows a known pattern of response to the test drug.
Probably Related	This category applies to those adverse events which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug.	An adverse experience may be considered probably related if or when (at least three of the following): • It follows a reasonable temporal sequence from administration of the drug. • It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • It follows a known pattern of response to the test drug.

Outcomes to Date are classified as follows:

- Recovered – The subject has fully recovered from the adverse event with no residual effects observable
- Recovered with sequelae – The subject has recovered from the adverse event with residual effects observable

- Recovering – the subject status improved but has been recovered
- Ongoing – AE is not recovered
- Fatal
- Unknown

AEs will be coded by Data Management using the using the Medical Dictionary for Regulatory Activities (MedDRA).

9.2 SERIOUS ADVERSE EVENTS (SAEs)

An SAE is any AE occurring at any dose that suggest a significant hazard or side effect, regardless of the Investigator or Sponsor's opinion on the relationship to the investigational product and that results in, but may not be limited to, any of the following outcomes:

- death (regardless of the cause)
- a life-threatening adverse event or suspected adverse reaction
- inpatient hospitalization or prolongation of existing hospitalization (any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility)
- a persistent or significant disability/incapacity or a substantial disruption of the ability to conduct normal life functions
- a congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be **serious** when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event.

Hospitalization for elective treatment of a pre-study condition that did not worsen while on study and optional hospitalizations not associated with a clinical adverse event (e.g., elective cosmetic surgery) are not considered SAEs.

Significant medical events are those which may not be immediately life-threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; resulting in an AE will normally be considered serious by this criterion.

A **life-threatening** adverse drug experience is any adverse event that places the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

9.3 DEFINITION OF AN UNEXPECTED ADVERSE EVENT

An **unexpected** adverse event is any adverse event, the specificity or severity of which is not consistent with information in the clinical protocol or current Investigator's Brochure for an

unapproved investigational product or package insert/summary of product characteristics for an approved product (package inserts are available separately at the participating center).

Suspected Unexpected Serious Adverse Reaction (SUSAR) is a serious adverse reaction assessed as unexpected by the Sponsor and that is judged by either the reporting investigator or the Sponsor to have a reasonable causal relationship to a medical product.

9.4 NOTIFICATION OF SERIOUS OR UNEXPECTED ADVERSE EVENT

Per FDA new safety reporting requirements (US Department of Health and Human Services September 2010)[30] a sponsor must continue to "promptly" review all safety information obtained from foreign or domestic sources. However, the sources of information listed in the regulation has expanded to include "any clinical or epidemiological investigations, animal or *in vitro* studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

If the Investigator identifies an SAE or Unexpected AE, an SAE report form must be completed and sent within 24 hours of the Investigator's knowledge of the event to the sponsor. The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

These preliminary reports will be followed within 24 hours by more detailed descriptions that will include a completed SAE form, copies of hospital case reports (i.e., hospital progress notes, results of applicable diagnostic tests, lab results and biopsy results), autopsy reports, and other documents, when requested and applicable.

For regulatory purposes, initial SAE reports submitted to SciVac immediately and should include:

a) a suspected investigational medicinal product

b) an identifiable subject (e.g., study subject code number)

c) an adverse event with a seriousness and the Investigator's assessment of the relationship to study drug

d) an identifiable reporting source (investigator contact details)

Once faxed or emailed, the printed SAE form and accompanying documentation should be placed in the SAE section of the Investigator's site file.

In addition, all AEs/SAEs/SUSARs will be reported to the IRB/IEC and regulatory authorities as required by local regulations and ICH-GCP guidelines.

Follow-up of SAEs/SUSARs

Follow-up of SAEs/SUSARs that occur during the study will continue until their satisfactory resolution or stabilization. In outstanding cases, it may be defined as "ongoing without further follow-up" by the Investigator and Sponsor's decision.

When supplementary information is available, a follow-up SAE Report Form must be completed by the site (marked as "follow-up report") and reported as indicated above.

Information to include on SAE form

The following information should be provided in the SAE form to accurately and completely record the event:

Investigator name and site address

Subject study identification number

Subject's initials

Subject demographics (gender, date of birth or age, weight, height)

Clinical Event:

- Description
- Date and time of onset, stop date, or duration
- Severity
- Treatment (including hospitalization)
- Relationship to study drug (causality)
- Action taken regarding study drug
- Information on recovery and any sequelae
- If the AE resulted in death
  - Cause of death (whether or not the death was related to study drug)
  - Autopsy findings (if available)
- Medical History case report form (copy)
- Concomitant Medication case report form (copy)
- Any relevant reports (laboratory, discharge, etc.)

Accompanying documentation, such as copies of hospital case reports, autopsy report, and other documents when applicable, should be sent as soon as they are available.

Subsequent additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded by the site to the Sponsor representative and study monitor within 24 hours of the information becoming available.

SAEs should also be reported to the IRB/IEC according to local regulations.

Subjects who have had an SAE during the treatment period must be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained.

Any newly emergent SAE after treatment is discontinued or the subject has completed the study and is considered to be related to the study drug or study participation should be recorded and reported immediately. The post-study period for the purpose of SAE reporting is up to 30 days following last visit of the study.

Follow-up Reports for non-serious AEs

All AEs, that do not meet any of the criteria for serious, should be regarded as non-SAEs. All AEs must be followed until resolution or stabilization and will be recorded on the Adverse Event Record in the CRF and if relevant, the Concomitant Medications Record in the CRF. Severity and relationship to study drug will be assigned by the Investigator as described in the section above.

9.5 ANTICIPATED ADVERSE EVENTS

Previous human experience and known adverse effects of the test product are detailed in the Product Information leaflet.

10 STATISTICAL METHODOLOGY

A total of 84 subjects, are expected to be recruited into study. The trial will follow-up eligible subject for a total duration of 12 months. One interim analysis is planned to be conducted at the time when approximately 50% of the subjects will reach Month 7 or early terminated the study.

10.1 INTERIM AND FINAL ANALYSES

One interim analysis is planned for possible early termination of the study.. The interim analysis will be performed at the time when approximately 50% of the subjects will reach Month 7 (1 month after the 3rd vaccine) or early terminated the study..

10.2 SIGNIFICANCE LEVEL

The overall significance level for this study will be 5% using two-tailed tests.

10.3 SAMPLE SIZE RATIONALE

Sample size determination was performed under the following assumptions:

- The primary endpoint for the study is the Seroprotection Rate (SPR), defined as the proportion of subjects with anti-HBs antibody titer at least equal to 10mIU/ml, at Month 7 (i.e. one month after the third immunization with Sci-B-Vac™). Subjects early terminated from the study for any reason at any time while having an anti-HBs antibody concentrations ≥ 10mIU/ml will be considered among those who met endpoint.
- It is expected that the true rate of SPR following treatment with Sci–B-Vac™ is 95% or more.
- The principal analysis of the primary endpoint will be a non-inferiority analysis testing the below hypothesis:
  - ✓ H_0: P-p_0 <= -Margin
  - ✓ H_1: P-p_0 > -Margin
- Where p0, the assumed true SPR is 95% and the non-inferiority margin is 9.0%, employing that study will be considered successful if the lower bound of the 95.0% exact CI will be 86.0% or more (lower non-inferiority limit).
- The rational for sample size calculation is based on demonstrating an expected SPR rate of 95%. The lower bound of a calculated 95% confidence interval (CI) using Exact binomial method ensures that the actual SPR rate will not exceed the calculated lower limit (will not be lower than the lower bound).
- The sample size is adjusted to a total of 84 subjects to account for an anticipated withdrawal rate of approximately 20%.

Sample Size Justification:

When the sample size is 70, a one-sided 95.0% confidence interval (CI) for a single proportion using Exact binomial method will demonstrate a lower bound of 86.0% or more for an expected proportion of 0.95.

10.4 ANALYSES SETS

10.4.1 Modified Intent-to-Treat (mITT) Analysis Set

The Modified Intent-to-Treat (mITT) analysis set is a subset of the ITT set. This set will consist of all enrolled subjects who were vaccinated at least once with Sci-B-Vac™ and had at least one post study IP administration follow-up visit. This analysis set will serve as the primary analysis set for efficacy and safety inference.

10.4.2 Full Treatment (FT) Analysis Set

The Full Treatment (FT) analysis set is a subset of the mITT analysis set and will consist of all subjects who were vaccinated 3 times with Sci-B-Vac™ and had at least one visit following the 3rd vaccination.

10.5 SUBJECT DISPOSITION

Data from subjects who are screened but not treated, subjects in the mITT, FT analysis sets, as well as study withdrawal data will be summarized using descriptive statistics. This summary will include all subjects screened into the study. The denominator for calculating the percentages will be the set of the mITT.

10.6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and baseline data as well as disease prognostic factors, medical history and prior medications will be summarized for the mITT analysis set using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation (SD), standard error, median, minimum, and maximum) will be provided. For categorical variables, subject counts and percentages will be provided. Categories for missing data will be presented if necessary. Missing categories will be presented if necessary.

10.7 EFFICACY ENDPOINTS AND ANALYSES

Analyses of primary and secondary efficacy endpoints will use the mITT Analysis Set including all enrolled subjects who were vaccinated at least once with Sci-B-Vac™ and had at least one post first Sci-B-Vac™ administration follow-up visit.

10.7.1 Primary Endpoint Definition and Analysis

The primary endpoint of the study is the Seroprotection rate (SPR), defined as the proportion of subjects with anti-HBs antibody titer at least equal to 10mIU/ml, at Month 7 (i.e. one month after the third immunization with Sci-B-Vac™). Subjects early terminated from the study for any reason at any time while having an anti-HBs antibody concentrations ≥ 10mIU/ml will be considered among those who met endpoint.

The principal analysis of the primary endpoint will employ a non-inferiority analysis [SAS PROC FREQ with binomial (noninf margin=0.09 p=(1-α) exact)] statement will be used for testing the below hypothesis:

H_0: P-p_0 <= -Margin

H_1: P-p_0 > -Margin

Where p_0, the assumed true SPR is 95% and the non-inferiority margin is 9.0%, employing that study will be considered successful if the lower bound of the (1-α) exact CI will be 86.0% or more.

10.7.2 Secondary Endpoints and Analyses

The secondary endpoints for the study are:

- SPR atone month after the first injection and at every month until Month 6 inclusive and at months 9 and 12.
- Percentage of subjects with anti-HBs antibodies titer ≥ 100mIU/ml at Month 0, and then at every month until Month 7 inclusive and at months 9 and 12.
-
- The geometric mean concentration (GMC) as determined by anti-HBsAg antibody titers at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.

SPR at all time points as above defined will be analyzed using the principal analysis method as above defined. The geometric mean concentration (GMC) as determined by anti-HBsAg antibody titers at Month 0, then at every month until Month 7 inclusive and at months 9 and 12 will be displayed across time in order to establish the kinetic of the immunological response during the study.

10.7.3 Exploratory Endpoints and analyses

The exploratory endpoints for the study are:

- The anti-preS1 antibody titers measured at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.
- The anti-preS2 antibody titers measured at Month 0, then at every month until Month 7 inclusive and at months 9 and 12.

The geometric mean concentration (GMC) at Month 0, then at every month until Month 7 inclusive and at months 9 and 12 will be displayed across time in order to establish the kinetic of the immunological response during the study.

10.8 DESCRIPTIVE STATISTICS

All measured variables and derived parameters will be listed individually and tabulated and descriptive statistics will be provided. For categorical variables summary tables will be provided displaying sample size, absolute and relative frequency and percentages. For continuous variables summary tables providing sample size, mean value or geometric means where appropriate, median, standard deviation (SD), standard error, minimum and maximum values. Summary statistics of Anti-HBs antibody concentrations and Anti-PreS1 and Anti-PreS2 antibodies concentrations will use geometric means due to the expected dispersion and skewness of the data.

Descriptive statistics for each of the study endpoints will be provided for the mITT Analysis Set and for both mITT and FT analyses set for the primary endpoint only.

10.9 SAFETY ASSESSMENTS

10.9.1 Treatment Emergent Adverse Events

Adverse events will be recorded from the time when a subject has signed the Informed Consent Form and throughout the study, including the follow-up period. The MedDRA dictionary will be used to standardize the terms used by the investigator to describe the Adverse Events. The following were incorporated into the analyses which will include only Treatment Emergent Adverse Events (TEAEs), namely, events that were started on the day of first study dose or afterwards.

- The incidence (no. of patients) and frequency (no. of events) of TEAEs broken down by SOC and by SOC and Preferred Term according to MedDRA dictionary.
- The incidence (no. of patients) and frequency (no. of events) of TEAEs broken down by events attributes.
- The derived dictionary used in the analyses.
- Listing of SAEs (regardless if started before or after first study dose) of randomized and dosed subjects captured in the clinical database until database drop date.
- Listing of Non-Treatment Emergent AEs.

10.9.2 Vital Signs

Vital signs will be measured at each treatment visit including at unscheduled or early termination visits. Analyses of vital signs were performed in the following manner:

- Box-Plots of vital signs before first study dose and afterwards by scheduled visit will be generated.
- Descriptive statistics of vital signs before first study dose and afterwards as well as the changes from baseline by scheduled visit will be generated.
- The incidence (no. of subjects) of potentially clinically significant (PCS) abnormal values will be summarized in a frequency table and will be listed.

10.9.3 Laboratory Evaluations

Analyses of safety laboratory data will be performed in the following manner:

- Box-Plots of laboratory measurements first study dose and afterwards by scheduled visit will be provided.
- Descriptive statistics of quantitative tests results and changes from baseline by scheduled visit.
- Quantitative laboratory measurements will be categorized with reference to the normal ranges as Low, Normal or High. Shift analysis of the categorical change form baseline to each scheduled visit and to the last observed assessment will also be presented.
- Incidence tables of PCS lab values as well as the individual subject listing will also be provided.

10.9.4 Other Safety Outcome Measures

Summary statistics of other safety evaluations including assessment of local safety evaluations and pain evaluations will be tabulated and listed. Kaplan-Meier curves will be used to describe time to study withdrawal.

10.10 Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the clinical study report, or any combination of these, as appropriate.

10.11 Statistical Software

Study accumulated data will be analyzed and summarized using the SAS® version 9.3(SAS Institute, Cary North Carolina) or higher.

11 ETHICS

11.1 Institutional Review Board or Independent Ethics Committee

Prior to initiation of the study, the Investigator will submit the study protocol and amendments, sample ICF, and any other documents that may be requested to the IRB/IEC for review and approval. The Investigator will request that the IRB/IEC provide written approval of the study and will keep on file records of approval of all documents pertaining to this study. The Investigator will not begin the study until the protocol and ICF have been approved by the IRB/IEC. The Investigator must agree to make any required progress reports to the IRB/IEC, as well as reports of SAEs, life-threatening conditions, or death.

11.2 Ethical Conduct of the Study

All clinical work conducted under this protocol is subject to GCP guidelines. This includes an inspection by Sponsor or its designee, health authority or IRB/IEC representatives at any time. The Investigator must agree to the inspection of study-related records by health authority representatives and/or Sponsor or its designee.

The study will be conducted in accordance with Sponsor's standards operating procedures and the following guidelines:

- GCP: Consolidated Guideline (International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- Declaration of Helsinki: Seoul, 2008
- Israeli Guidelines, Laws and Regulations for the conduct of clinical trials (2006)

11.3 Subject Information and Consent

Prior to screening for the study each subject will be informed in detail about the study drugs to be administered, and the nature of the clinical investigation with its risks and discomforts to be expected. The basic elements of informed consent as specified by the FDA (21 CFR 50.25) and ICH-GCP will be followed. The subjects will also be instructed that they are free to withdraw their

consent and discontinue their participation in the study at any time without prejudice. Written consent will be obtained from each subject to be involved in the clinical trial by using the IRB/IEC-approved ICF prior to the conduct of any study-related activity. A copy of the ICF will be submitted together with this protocol and must be approved by the IRB/IEC prior to study commencement. Each subject will be given a copy of the written ICF, and each subject's chart will include the signed ICF for study participation. The original subject signed and dated ICFs will be maintained by the site for 15 years. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having done so during the study.

11.4 SUBJECT INSURANCE

A product liability to cover against injury and damages arising from the use of products in this project is provided by SciVac for the total duration of the study covering the subjects and Investigators in respect of the risks involved in conducting this study according to this protocol. The insurance policy will be filed in the Investigator's site file or can be made available to the Investigator and to the IRB/IEC upon request.

Where applicable, subjects will be insured through contract between an insurance company and the Sponsor.

11.5 PERSONAL DATA PROTECTION

SciVac complies with the principle of subject's right to protection against invasion of privacy. Throughout this trial, all subject data will be identified only by a subject identification number and subject initials and date of birth. The data will be blinded in all data analyses. The subject must be informed and consent as required that authorized personnel on behalf of SciVac such as study monitor, auditor etc. and relevant health regulatory agency will have direct access to personal medical data to assure a high quality standard of the study.

At the subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

11.6 INFORMING THE GENERAL PRACTITIONER

The Investigator will inform the subject's primary care physician of the subject's participation in the study, by sending a letter to the physician as required by the Israeli Guidelines for the Conduct of Clinical Trials.

11.7 PROTOCOL EXCEPTIONS AND DEVIATIONS

It is expected that subjects will meet all eligibility criteria as specified in the protocol. Deviations from the protocol should be avoided, unless required for the safety of the subject. Protocol deviations, and if possible the reason for occurrence, will be documented by the study monitor and will be included in the final clinical study report. The Investigator must report any protocol deviation to the Sponsor and if required, to the IRB/IEC in accordance with local regulations, within reasonable time.

11.8 PROTOCOL AMENDMENTS

All protocol modifications must be submitted to the site IRB/IEC in accordance with local requirements and, if required, to the Regulatory Authority, either as an amendment or a notification.