STATISTICAL ANALYSIS PLAN

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

Protocol Version 3.0 amendment #2 dated 01-05-2016

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SUMMARY OF SECTIONS

1. ABBREVIATIONS

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
IRB	Institutional Review Board
Kg	Kilogram
m	Meter
MedDra	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mITT	Modified intention-to-treat analysis
ml	Milliliter
MOH	Ministry of Health
N/A	Not Applicable
ºC	Degrees centigrade
PI	Principal Investigator
PT	Prothrombin Time
PT	Preferred Term

PT/INR	Prothrombin time/International Normalized Ratio
QA	Quality Assurance
R&D	Research and Development
RBC	Red blood cells
RDW	RBC distribution width
RR	Respiration rate
SAS	Statistical Analysis Software
SAE	Serious Adverse Event
SOC	System Organ Class
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

2. INTRODUCTION

2.1 Objectives

This document details the statistical analysis that will be performed for the SciVac Ltd. Phase IV study SciB018.

The study primary objective is:

- 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.

The secondary objectives are:

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

The Exploratory Objectives are:

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

2.2 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 section 2.3).

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 the study protocol.

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.

2.3 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)*	*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
Smoking status	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[14]	X[14, 15]	X[15]				X[14]	X[15]		
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[6]	X[6]	X	X	X	X	X[6]	X	X	X
Sample for further investigations		X[6]	X[6]	X	X	X	X	X[6]	X	X	X
Adverse Events	Recorded throughout the study										
Concomitant Medications	Recorded throughout the study										

1 ± 3 days (Visit2/Treatment 1 may be performed up to 4 weeks +3 days from screening visit)
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 (also markers for previous vaccination), 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
14 Local reaction grading after vaccination
15 Local reaction grading of previous vaccine administration and follow up until symptoms resolve

2.4 Study Populations

Up to ninety two (92) healthy subjects will be enrolled in the study

Intent-to-Treat (ITT) Population includes all enrolled subjects who were vaccinated at least once with Sci-B-Vac™. The Safety population will be same as ITT population.

Modified Intent-to-Treat (**mITT**) **population** 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 vaccination follow-up visit, fully comply with the study protocol, had no violation of any of the inclusion/exclusion criteria and did not demonstrate an anamnestic response after the 1st administration of Sci-B-Vac. An anamnestic response revealed by Sci-B-Vac is defined as anti-HBs level above 6000mIU/ml (the highest titer recorded upon Sci-B-Vac 1st injection) in a subject with no detectable anti-HBs antibody at visits 1 and 2. Subjects who early terminated the study but reached the primary endpoint will be included as well. Subjects who did not complete the full-course of vaccination (i.e. 3 injections) and did not reach SPR will be excluded from the mITT set. This analysis set will serve as the primary analysis set for efficacy and safety inference.

Full Treatment (FT) 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.

2.5 Study 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 one month after the first injection 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:

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.

2.6 Sample size

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:

  H0: P-p0 ≤ -Margin

  H1: P-p0 > -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 rationale 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 94 subjects to account for an anticipated withdrawal rate of approximately 20%.
- The sample size was enlarged to 92, to ensure sufficient sample size is achieved upon the exclusion of isolated case of anamnestic response. An anamnestic response revealed by Sci-B-Vac is defined as anti-HBs level above 6000mIU/ml (the highest titer recorder upon Sci-B-Vac 1st injection in naïve subject) in eligible subject with no detectable anti-HBs antibody at visits 1 and 2.

<u>Sample Size Justification:</u>

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.

2.7 Interim Analyses

The percent of subjects who achieved the primary endpoint will be tested at various time points. As soon as approximately 95% of the subjects (from at least 50 subjects) will be found seroprotected (having anti-HBs antibody concentrations ≥ 10mIU/ml) then the primary efficacy endpoint will be achieved and the analysis will be considered a formal interim analysis and will be reported. A second interim analysis will be performed after all subjects have completed all three injections. Subjects who early terminated the study but reached the primary endpoint prior to termination will be included in the analysis.

Interim analysis reports will include all efficacy and safety information collected up to the interim analysis cut-off date. Exploratory endpoints (anti-pre-S1 and anti-pre-S2 testing) will not be included in the interim reports.

2.8 Final Analyses

The final analysis will include all the subjects who completed 12 months of follow-up, fully comply with the study protocol and have no inclusion/exclusion criteria violation. Subjects who early terminated the study but achieved the primary endpoint prior to withdrawal will be included as well (mITT population). If 95% of the subjects will be found seroprotected (having anti-HBs antibody concentrations ≥ 10mIU/ml) then the primary endpoint will be achieved.

3. STATISTICAL METHODS

3.1 General

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

The data will be analysed using the SAS ® version 9.3 or higher (SAS Institute, Cary North Carolina).

3.2 Data Summaries

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics.

3.3 Continuous

For continuous variables summary tables will be provided giving sample size, arithmetic mean, standard deviation, standard error, median, minimum and maximum and 95% confidence interval for means (id appropriate). 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.

3.4 Categorical

For categorical variables summary tables will be provided giving sample size, absolute and relative frequency.

3.5 Protocol Deviations

Listing of protocol deviations will be provided.

4. ANALYSIS PLAN

4.1 Introduction

All summaries and analyses documented below will be presented in the final integrated statistical/clinical report and tables that will be based on the E3 guidelines published by ICH. However, it is noted here that no analysis plan prepared in advance of database lock can be absolutely definitive and so the final report may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final report.

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.

4.1 Disposition of Subjects

Data from subjects who are screened but not treated, subjects in the ITT, 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 ITT.

4.2 Demographics and Baseline Characteristics

Demographic and baseline data as well as disease prognostic factors, medical history and prior medications will be summarized for the ITT analysis set using appropriate descriptive statistics. Baseline characteristics (age, BMI and smoking status) will be presented by categories used for efficacy analyses. Categories for missing data will be presented if necessary. Missing categories will be presented if necessary.

The proportion of subjects who recorded concomitant medications will be tabulated

4.3 Compliance

Summary table of compliance data based on Sci-B-Vac injections will be generated for the ITT analysis set.

4.4 Primary Endpoint 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™). In the first Interim Analysis the primary endpoint will be tested on month 4. 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:

H0: P-p0 ≤ -Margin
H1: P-p0 > -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 (1-α) exact CI will be 86.0% or more.

The rate of responders will be calculated along with 95% confidence interval using Exact binomial method. The final population for statistical analysis will include only subjects who fully comply with the study protocol, have no inclusion/exclusion criteria violation and subjects who early terminated the study but reached the primary endpoint prior to withdrawal (mITT population).

Comparative analysis will be applied for baseline characteristics (such as gender, smoking status, age and BMI) between non seroprotected subjects (i.e. anti-HBsAg antibody<10), seroprotected subjects (ie. anti-HBsAg antibody≥10 mIU/ml) and subjects with Anti-HBs≥100 mIU/ml.

Age categories will be defined by intervals of 5 or 10. BMI will be defined <25 or ≥25. Smoking status will be defined using 5 categories:

Never

Past-smoker;

Light smoker (up to 10 cigs/day)

Moderate smoker (10-19 cigs/day)

Heavy smoker (20 or more cigs/day)BMI categories will be defined <25 and ≥25

4.5 Secondary Endpoints Analysis

The secondary endpoints for the study are:

- SPR one 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 ≥ 100
- mIU/ml one month after the first injection 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 defined above will be analyzed using the principal analysis method as defined for the primary endpoint, and will be presented graphically as well.

The percentage of subjects with anti-HBs antibodies titer ≥ 100 mIU/ml will be calculated from the responders sub-set at each available time-point. Subjects with titer>10 mIU/ml and <100 mIU/ml will be defined 'low-responders'.

The geometric mean concentration (GMC) as determined by anti-HBsAg antibody titers one month after the first injection and at every month until Month 7 inclusive and at months 9 and 12 will be calculated with 95% confidence intervals. Graphical presentation of GMC by month will be generated.

4.6 Exploratory Endpoints Analysis

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.

4.7 Safety analysis

4.7.1 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 have started on the day of first study dose or afterwards.

- Summary incidence of adverse events.
- The incidence (no. of subjects) and frequency (no. of events) of TEAEs broken down by System Organ Class (SOC) and by Preferred Term (PT) according to MedDRA dictionary.
- The incidence (no. of subjects) and frequency (no. of events) of TEAEs by SOC, PT and by Severity of event.
- The incidence (no. of subjects) and frequency (no. of events) of TEAEs by SOC, PT and by Relation to study drug.
- The derived dictionary used in the analyses (listing of full glossary).
- 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.

4.7.2 Vital Signs

Vital signs will be measured at each treatment visit including at screening and early termination visits whereas unscheduled visit is optional. Analyses of vital signs will be performed in the following manner:

- Descriptive statistics of vital signs before first study dose and afterwards as well as the changes from baseline by scheduled visit will be generated.
- Vital signs will be graded based on table 2 in appendix C of the protocol:

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 - BPM	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - BPM	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

- The incidence (no. of subjects) of vital signs grading will be summarized in a frequency tables.
- Box-Plots of vital signs before first study dose and afterwards by scheduled visit will be provided by request for specific parameters. .

4.7.3 Laboratory Test Results

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

- 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. Incidence tables of laboratory results categories will be presented by visit.
- Incidence tables of CS lab values defined by the PI as well as the individual subject listing will also be provided.
- Box-Plots of laboratory measurements from first study dose and afterwards by scheduled visit will be provided by request for specific parameters.

4.7.4 Other Safety Assessments

Summary statistics of other safety evaluations including assessment of ECG, local safety evaluations and pain evaluations (i.e. local reaction grading) will be tabulated and listed.

5. APPENDIX I: TABLES TO BE INCLUDED IN THE STATISTICAL REPORT

Table number	Table Title
14.1	**Demographic and Baseline Data**
14.1-1.1	Disposition of subjects
14.1-1.2	Primary reason for early discontinuation
14.1-2.1	Analysis population
14.1-3.1	Demographic and Baseline data, ITT
14.1-4	Medical History, ITT
14.1-5	Baseline Physical Examination, ITT
14.1-6	Any Concomitant Medication, ITT
14.1-7	Any Concomitant Non-drug Medication, ITT
14.1.2	**Exposure to Sci-B-Vac injection**
14.1.2.1	Sci-B-Vac injection, ITT
14.2	**Efficacy Analysis**
14.2-1	Seroprotection rate (SPR) by Month, mITT
14.2-2	Seroprotection rate (SPR) by Month, FT (for first IA mITT who completed month 7 will be presented)
14.2-3	Secondary Endpoint Analysis: Percentage of Subjects with Anti-HBs≥100 mIU/ml by Month, mITT
14.2-4	Secondary Endpoint Analysis: Percentage of Subjects with Anti-HBs≥100 mIU/ml) by Month, FT (for first IA mITT who completed month 7 will be presented)
14.2-5	Geometric means of anti-HBs antibody titers by month, mITT
14.2-6	Geometric means of anti-HBs antibody titers by month, FT (for first IA mITT who completed month 7 will be presented)
14.2-7	Frequency of gender by responders (SPR) (at month 4 for first IA)
14.2-8	Frequency of age categories by responders (SPR) (at month 4 for first IA)
14.2-9	Frequency of Responders (SPR) by Smoking status and month (month 4 for IA)
14.2-10	Frequency of Responders (SPR) by BMI categories and month (at month 4 for first IA)
14.2-11	Geometric means of anti-HBs antibody titers by month and Gender
14.2-12	Geometric means of anti-HBs antibody titers by month and age categories
14.2-13	Geometric means of anti-HBs antibody titers by month and Smoking status
14.2-14	Geometric means of anti-HBsAg antibody titers by month and BMI categories
14.2-15	Serologic Markers for Hepatits B Infection, ITT
14.3	**Safety Data**
14.3.1	**Adverse Events**
14.3.1	Summary Incidence of TEAE (Treatment Emergent Adverse Events), ITT
14.3.1-1	Summary of Adverse Events by SOC and PT, ITT

Table number	Table Title
14.3.1-2	Summary of Adverse Events by SOC and PT and Severity, ITT
14.3.1-3	Summary of Adverse Events by SOC and PT and Relation to study drug, ITT
14.3.1-4	Summary of Serious Adverse Events by SOC and PT, ITT
14.3.2	**Listing of SAEs** (if applicable)
14.3.2-1	Listing of Serious Adverse Events
14.3.4	**Abnormal Laboratory Results**
14.3.4-1	Incidence of Hematology Abnormal Clinically Significant Results
14.3.4-2	Out of Range Hematology Results
14.3.4-3	Incidence of Chemistry Abnormal Clinically Significant Results
14.3.4-4	Out of Range Chemistry Results
14.3.4-5	Incidence of Urinary Abnormal Clinically Significant Result
14.3.4-6	Out of Range Urinary Result
14.3.4-7	Pregnancy test (Females)
14.3.5	**Other Safety Assessment**
14.3.5	Summary statistics of Hematology results by Visit
14.3.6	Summary statistics of Hematology Changes from Baseline by Visit
14.3.7	Summary statistics of Chemistry results by Visit
14.3.8	Summary statistics of Chemistry Changes from Baseline by Visit
14.3.9	Summary statistics of Urinalysis results by Visit
14.3.10	Summary statistics of Urinalysis Changes from Baseline by Visit
14.3.11	Summary of Vital Signs by Visit
14.3.12	Frequency of Vital Signs Grading by Visit
14.3.13	Summary of Vital Signs Changes from Baseline (pre-vaccination) by Visit
14.3.14	ECG Assessment
14.3.15	Local Reaction
14.3.16	Any Change in Subject's Health and in concomitant medications since last visit

6. APPENDIX II: LISTINGS TO BE INCLUDED IN THE STATISTICAL REPORT

Listing number	Listing Title
16.2	**Listings by Subject**
16.2.1	**Disposition of Subjects**
16.2.1-1	Disposition of subjects, ITT
16.2.4	**Demographic, baseline and Medical History data**
16.2.4-1	Demographic and baseline data
16.2.4-2	Medical History
16.2.4-2a	Reported Medical History for Screening Failures
16.2.4-3	Baseline Physical Examination
16.2.4-4	Concomitant Medications
16.2.4-5	Concomitant Non-drug Treatments
16.2.4-6.1	Serology Markers for Hepatitis B Infection at Screening/ Visit 11/ET
16.2.4-6.2	Early Serology Markers for Hepatitis B Infection monitored during the study
16.2.5	**Exposure to Sci-B-Vac Injection**
16.2.5-1	Compliance data
16.2.6	**Individual Efficacy response data**
16.2.6-1	Serologic Response to Immunization
16.2.7	**Adverse event listings**
16.2.7-1	Treatment Emergent Adverse Events
16.2.7-2	Non-Treatment Emergent Adverse Events
16.2.7-3	Full Glossary of Adverse Events
16.2.8	**Listing of individual laboratory and other assessments by subject**
16.2.8-1	Abnormal Clinically Significant Hematology Results
16.2.8-2	Hematology Results
16.2.8-3	Abnormal Clinically Significant Chemistry Results
16.2.8-4	Chemistry Results
16.2.8-5	Abnormal Clinically Significant Urinalysis Results
16.2.8-6	Urinalysis Results
16.2.8-7-1	Test for Pregnancy (Females)
16.2.8-7-2	Previous pregnancies data for subject S1168
16.2.8-7.3	Current pregnancy data for subject S1168
16.2.8-8	Vital Signs
16.2.8-9	ECG Assessment
16.2.8-10	Local Reaction grading
16.2.8-11	Any Change in subject's health and in concomitant medications since last visit
16.4	**Eligibility**
16.4-1	Inclusion/ Exclusion Criteria

Listing number	Listing Title
16.4.2	**Visit dates**
16.4.2-1	Visit dates per Subject
16.4.4-1	Protocol deviations

7. APPENDIX III: FIGURES

Figure number	Title
Figure 1	SPR by month, mITT
Figure 2	SPR by month, FT (for first IA mITT who completed Month 7)
Figure 2.1	Percentage of non-responder, responder and high-responder to Sci-B-Vac™ by Month, mITT (second interim analysis)
Figure 3	Geometric Mean of anti-HBs Antibody titers by month, mITT
Figure 4	Geometric Mean of anti-HBs Antibody titers by month, FT (for first IA mITT who completed Month 7)
Figure 5	Geometric Mean of anti-HBs Antibody titers by month and Gender
Figure 6	Geometric Mean of anti-HBs Antibody titers by month and Age
Figure 7	Geometric Mean of anti-HBs Antibody titers by month and Smoking status
Figure 8	Geometric Mean of anti-HBs Antibody titers by month and BMI

* Box plots for laboratory results and vital signs will be generated for specific parameters, based on the results and the sponsor's request.

8. APPENDIX IV: LISTINGS OF SCREENING FAILURES

Listing number	Listing Title
18.1	**Demographic and Baseline data**
18.2.4-1	Demographic and baseline data
18.2.4-2	Medical History
18.2.4-3	Baseline Physical Examination
18.2.4-6	Baseline Serology Markers for Hepatitis B Infection
18.2.5	**Reasons for Screening Failure**
18.2.5	Reasons for Screening Failure
Table 18.2.5	Summary of Reasons for Screening Failure
18.2.8	**Listing of individual laboratory and other assessments by subject**
18.2.8-2	Hematology Results
18.2.8-4	Chemistry Results
18.2.8-6	Urinalysis Results
18.2.8-7	Pregnancy Blood Test (Females)
18.2.8-8	Vital Signs
18.2.8-9	ECG Assessment
18.2.8-10	Screening Serology

9. VERSION HISTORY:

Version	Date	Section	Changes	Done By
1.0	22/Feb/2016		Original Release	
1.1	23/Jun/2016	abbreviations	Added/deleted abbreviations	Daphna Goffer/ Nathalie Machluf
		2.3	Study flow chart was revised according to changes in the protocol	
2.0	23/Jul/2016	4.4	Added analyses by gender, age, BMI and smoking, Defining age, BMI and smoking categories	Daphna Goffer/ Nathalie Machluf
		4.5	Adding figures for SPR, GMC Delete GMC ratio	
		2.7	Update interim analysis report description	
3.0	18/Sep/2016	Appendix I and II	Minor edits to tables and listings names/tables	Daphna Goffer/ Nathalie Machluf
		4.7.2	Add text to table 2 (vital signs grading)	
4.0	24/May/2017	2.7	Adding second Interim Analysis	Daphna Goffer
		Appendix I and III	Minor edits to tables names	
		Appendix II	Correct order of listings Add listings 16.2.8-7-2 and 16.2.8-7-3	

10. APPROVAL FOR IMPLEMENTATION OF

Statistical Analysis Plan

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™**
Reference:	**SciB018 SAP**
Version:	**V4.0**
Date effective:	**25-May-2017**
Author:	**Daphna Goffer Statistician, Medistat**
Author's signature:	**Date: 25 May 2017**
Reviewed By:	**Gil Harari, CEO Statistician, Medistat**
Reviewer's signature:	**Date: 25 May 2017**

The above Statistical Analysis Plan has been reviewed and approved by the Sponsor:

Name of Approver: **Nathalie Machluf**

Position: **Director Clinical and Regulatory Affairs**

Signature:  Date: 25/5/2017